8 Potassium

Lisa M. Satlin

Potassium is the most abundant intracellular cation. Approximately 98% of the total body potassium content is located within cells, primarily muscle, where its concentration ranges from 100–150 mEq/L; the remaining 2% resides in the extracellular fluid, where the potassium concentration is tightly regulated within a narrow range (3.5–5.0 mEq/L in the adult). The ratio of the intra- to extracellular potassium concentration determines, in large part, the resting membrane potential, and is thus critical for normal function of electrically excitable cells, including nerve and muscle. Maintenance of a high intracellular potassium concentration is essential for many cellular processes, including DNA and protein synthesis, cell growth and apoptosis, mitochondrial enzyme function, and conservation of cell volume and pH (1–7). Because of the many vital processes dependent on potassium homeostasis, multiple complex and efficient mechanisms have developed to regulate total potassium balance and distribution.

Potassium Homeostasis

Total body potassium content reflects the balance between intake and output, the latter regulated primarily by renal and, to a lesser extent, fecal excretion; the amount of potassium lost through sweat is negligible. The homeostatic goal of the healthy adult is to remain in zero potassium balance. Thus, ~90% of the daily potassium intake, which typically averages 1 mEq/kg body weight, is eliminated by the kidneys and the residual ~10% lost through the stool (8).

Total body potassium content increases from approximately 8 mEq/cm body height at birth to >14 mEq/cm body height by 18 years of age (9, 10) (*Fig. 8-1*), with the rate of accumulation of body potassium per kilogram body weight in the infant exceeding that in the older child and adolescent. The increase in total body potassium content correlates with an increase in cell number and potassium concentration (at least in skeletal muscle) with advancing age (10–12). This robust somatic growth early in life requires the maintenance of a state of positive potassium balance (13, 14), as has been demonstrated in growing infants greater than approximately 30 weeks gestational age (GA) (15, 16). The tendency to retain potassium early in postnatal life is reflected, in part, in the higher plasma potassium values in infants, and particularly in preterm neonates (16, 17).

Thirty to fifty percent of very low birth weight and premature infants < 28 weeks GA exhibit nonoliguric hyperkalemia, defined as a serum potassium concentration of >6.5 mEq/L, during the first few days of life, despite the intake of negligible amounts of potassium (18–22). This phenomenon, not observed in mature infants or VLBW infants after 72 h (20, 21), has been proposed to reflect principally an intra- to extracellular shift of potassium (20, 21, 23). Prenatal steroid treatment may prevent this nonoliguric hyperkalemia via induction of sodium-potassium-adenosine triphosphatase (Na-K-ATPase) activity (see below) in the fetus (24, 25).

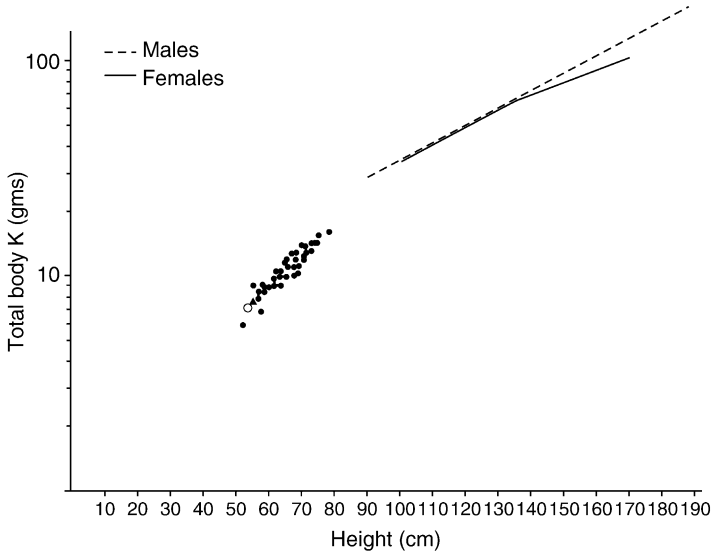
Studies in rats suggest that the accumulation of potassium in the growing fetus is facilitated by the active transport of potassium across the placenta from mother to fetus (26). This notion is further supported by studies in dog (27) and rat (28) that show that fetal plasma potassium concentrations are maintained during maternal hypokalemia, an adaptation proposed to be due to an increase in the ratio of maternofetal-to-fetomaternal unidirectional potassium transport.

Regulation of Internal Potassium Balance

The task of maintaining potassium homeostasis is challenging because the daily dietary intake of potassium in the adult (~50–100 mEq) approaches or exceeds the total potassium normally present within the extracellular fluid space (~70 mEq in 17 L of extracellular fluid with a potassium concentration averaging ~4 mEq/L). To maintain zero balance in the adult, all the dietary intake of potassium must be ultimately eliminated, a task performed primarily by the kidney. However, excretion of potassium by the kidney is sluggish. Only 50% of an oral or intravenous load of potassium is excreted during the first 4–6 h after it is administered (29, 30). Life-threatening

Figure 8-1

Relationship between total body potassium (gm) and height (cm) for infants and children. The rate of accretion of body potassium in the neonate is faster than in later childhood, likely reflecting both an increase in cell number and potassium concentration, at least in skeletal muscle, with advancing age (10).



hyperkalemia is not generally observed during this period because of the rapid (within minutes) hormonally mediated translocation of ~80% of the retained potassium load from the extracellular space into cells (31). The buffering capacity of the combined cellular storage reservoirs, which includes muscle, bone, liver, and red blood cells (RBCs), is capable of sequestering up to approximately 3,500 mEq of potassium and is vast compared with the extracellular pool (8).

Cells must expend a significant amount of energy to maintain the steep potassium (and sodium) concentration gradients across their cell membranes. This is accomplished by the ubiquitous Na-K-ATPase which transports 3 sodium ions out of and 2 potassium ions into the cell at the expense of the hydrolysis of cytosolic ATP. The unequal cation exchange ratio produces a charge imbalance across the cell membrane, and thus the Na-K-ATPase is defined as an electrogenic pump. Positively charged potassium ions, present in high concentration within the cell, passively leak out of cells down a concentration gradient through ubiquitously expressed potassium-selective channels. A steady state is reached at which the outward movement of positively charged potassium is opposed by the negative cell potential. At this cell equilibrium potential, the net transmembrane flux of potassium is zero.

The basic functional unit of the Na-K-ATPase is comprised of a catalytic α and a β subunit; the β subunit acts a molecular chaperone that directs the correct membrane insertion of the α subunit (32). The α/β-heterodimer complexes with phospholemman (PLM, FXYD1) in heart and skeletal muscle (33); the latter interaction modulates pump activity (33). The cardiac glycoside digoxin binds to the catalytic α subunit of the enzyme, inhibiting its activity. Thus, digoxin overdose may thus be associated with hyperkalemia, especially in the presence of a concomitant perturbation of potassium homeostasis.

Na-K-ATPase is regulated by changes in its intrinsic activity, subcellular distribution, and cellular abundance. Long-term stimulation of pump activity is generally mediated by changes in gene and protein expression, whereas short-term regulation typically results from changes in the intracellular sodium concentration, alterations in the phosphorylation status of the pump and/or interaction with regulatory proteins, or changes in membrane trafficking of preexisting pumps (33–35). Regulation of internal potassium balance in the neonate may be influenced by developmental stage-specific expression of potassium transporters, such as Na-K-ATPase, as well as channels, receptors, and signal transduction pathways (36, 37).

The chemical, physical, and hormonal factors that acutely influence the *internal* balance of potassium are listed in *Table 8-1*, and are discussed below. Potassium uptake into cells is acutely stimulated by insulin, β_2-adrenergic agonists, and alkalosis and is impaired by α-adrenergic agonists, acidosis, and hyperosmolality. Generally, deviations in extracellular potassium concentration

Table 8-1

Factors that regulate internal potassium balance and their effects on cell uptake of potassium

Physiologic factors	
Plasma K concentration	
Increase	Increases uptake
Decrease	Decreases uptake
Insulin	Increases uptake
Catecholamines	
α-Agonists	Decreases uptake
β-Agonists	Increases uptake
Pathologic factors	
Acid-base balance	
Acidosis	Decreases uptake
Alkalosis	Increases uptake
Hyperosmolality	Enhances cell efflux
Cell breakdown	Enhances cell efflux

arising from fluctuations in internal distribution are self-limited as long as the endocrine regulation of internal balance and mechanisms responsible for regulation of *external* balance are intact.

Plasma Potassium Concentration

Active basolateral cellular potassium uptake by the ubiquitous Na-K-ATPase in large part determines the intracellular pool of potassium. An increase in potassium input into the extracellular fluid space, which may arise from exogenous or endogenous sources or result from a chronic progressive loss of functional renal mass, decreases the concentration gradient against which the Na-K-ATPase must function and thus favors an increase in cellular potassium uptake. Sources of exogenous potassium input may not be readily apparent and include not only diet, but also potassium-containing drugs (potassium penicillin G), salt substitutes, protein-calorie supplements, herbal medications and packed RBCs (38). The extracellular fluid potassium concentration can also increase in response to endogenous release of potassium as accompanies tissue breakdown (rhabdomyolosis, tumor lysis syndrome) and exercise, the latter mediated by adenosine triphosphate (ATP) depletion and opening of ATP-dependent potassium channels. In those epithelial cells of the kidney and colon specifically responsible for potassium secretion, the resulting increase in intracellular potassium maximizes the concentration gradient between cell and lumen, thereby promoting potassium diffusion into the tubular lumen and thus potassium excretion.

Hormones

Insulin, the most important hormonal regulator of internal potassium balance, stimulates Na-K-ATPase-mediated cellular potassium uptake and thus the rapid transfer of potassium from the extracellular to the intracellular fluid space of insulin-responsive cells in liver, skeletal muscle, adipocytes, and brain, a response that is independent of the hormonal effects on glucose metabolism (39). The mechanism of insulin action in these tissues differs, in part, because of differences in the isoform composition of the catalytic α-subunit of the pump. Insulin stimulates Na-K-ATPase activity by promoting the translocation of preformed pumps from intracellular stores to the cell surface (40–44), and/or increasing cytoplasmic sodium content (45–47) or the apparent affinity of the enzyme for sodium (48).

Basal insulin secretion is necessary to maintain fasting plasma potassium concentration within the normal range (29). An increase in plasma potassium in excess of 1.0 mEq/L in the adult induces a significant increase in peripheral insulin levels to aid in the rapid disposal of the potassium load, yet a more modest elevation of approximately 0.5 mEq/L is without effect (29, 49, 50). In the setting of insulin deficiency, i.e., diabetes, there is a reduction in uptake of potassium by muscle and liver (31, 51).

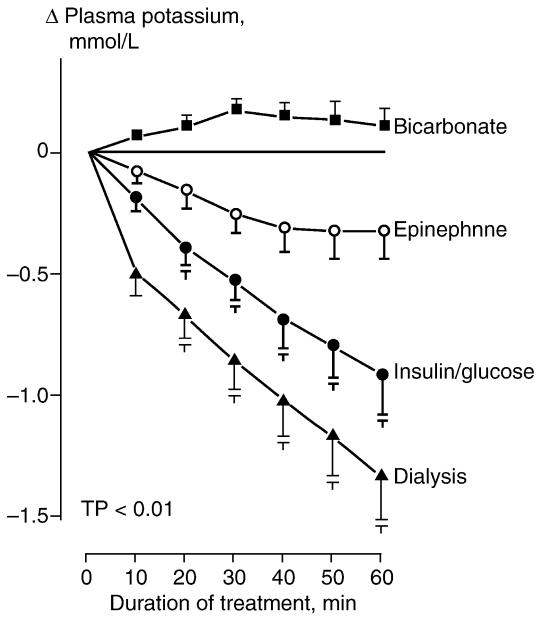
Catecholamines enhance the cell uptake of potassium via stimulation of Na-K-ATPase activity in skeletal muscle and hepatocytes through β_2-adrenergic receptors (52, 53). The effect of epinephrine on potassium balance in the adult is biphasic and is characterized by an initial increase, followed by a prolonged fall in plasma potassium concentration to a final value below baseline. The initial transient rise in plasma potassium results from α-adrenergic receptor stimulation which causes release of potassium from hepatocytes and impairs cell uptake of potassium (51, 54–56). β_2-Receptor stimulation, via stimulation of adenylate cyclase leading to generation of the second messenger cyclic adenosine monophosphate (cAMP) and activation of downstream protein kinases, stimulates the sodium pump and thus promotes enhanced uptake of potassium by skeletal and cardiac muscle, effects that are inhibited by nonselective β-blockers including propranolol and labetalol (51, 55, 57–60). The observation that the potassium-lowering effects of insulin and epinephrine are additive suggests that their responses are mediated by different signaling pathways.

The effects of these hormones on the distribution of potassium between the intracellular and extracellular compartments have been exploited to effectively treat disorders of homeostasis (*Fig. 8-2*). Administration of β_2-adrenoreceptor agonists (albuterol or salbutamol via nebulizer), which promote potassium uptake by cells, has been to treat hyperkalemia in neonates, children and adults (62–64). A single dose of nebulized albuterol can lower serum potassium by as much as 0.5 mEq/L (65, 66). Transient side effects associated with this class of drugs include mild tachycardia, tremor and mild vasomotor flushing (67). Administration of glucose alone (to induce endogenous insulin release) or glucose plus insulin is efficacious, although patients must be monitored for complications of hyperglycemia (without insulin) or hypoglycemia (with insulin), especially in neonates (68–70). It should be kept in mind that the treatment options discussed thus far are only temporizing. To remove potassium from the body, renal potassium excretion must be enhanced, either by stimulating potassium secretion in the distal nephron (see below) or, in the presence of renal insufficiency, by dialysis.

Aldosterone is best known for its effect on transporting tissue, increasing potassium secretion in distal segments of the nephron and colon (see below). Triiodothyronine (T3) also promotes Na-K-ATPase-mediated potassium cellular uptake in skeletal muscle (34). Whereas T3 had been thought to act as a direct transcriptional activator of target genes, recent studies emphasize the importance of nongenomic effects, including the stimulation of translocation of Na-K-ATPase to the plasma membrane by a pathway that requires activation of MAPK and phosphatidylinositol 3-kinase (PI3K) (71, 72). The postnatal increases in Na-K-ATPase expression in kidney, brain, and lung depend on normal thyroid hormone status (73).

Figure 8-2

Changes in plasma potassium concentration (mmol/L) during intravenous infusion of bicarbonate (8.4%), epinephrine, or insulin and glucose, and during hemodialysis in adult patients on maintenance hemodialysis (61).



Acid–Base Balance

It is well known that the transcellular distribution of potassium and acid-base balance are interrelated (74–77). Whereas acidemia (increase in extracellular hydrogen ion concentration) is associated with a variable increase in plasma potassium secondary to potassium release from the intracellular compartment, alkalemia (decrease in extracellular hydrogen ion concentration) results in a shift of potassium into cells and a consequent decrease in plasma potassium. However, the reciprocal changes in plasma potassium that accompany acute changes in blood pH differ widely among the four major acid-base disorders; metabolic disorders cause greater disturbances in plasma potassium than do those of respiratory origin, and acute changes in pH result in larger changes in plasma potassium than do chronic conditions (74).

Acute metabolic acidosis after administration of a mineral acid that includes an anion that does not readily penetrate the cell membrane, such as the chloride of hydrochloric acid or ammonium chloride, consistently results in an increase in plasma potassium. As excess extracellular protons, unaccompanied by their nonpermeant anions, enter the cell where neutralization by intracellular buffers occurs, potassium is displaced from the cells, thus maintaining electroneutrality and leading to hyperkalemia. However, comparable acidemia induced by acute organic anion acidosis (lactic acid in lactic acidosis, acetoacetic and β-hydroxybutyric acids in uncontrolled diabetes mellitus) may not elicit a detectable change in plasma potassium (74, 78, 79). In organic acidemia, the associated anion diffuses more freely into the cell and thus does not require a shift of potassium from the intracellular to the extracellular fluid.

In respiratory acid-base disturbances, in which carbon dioxide and carbonic acid readily permeate cell membranes, little transcellular shift of potassium occurs because

protons are not transported in or out in association with potassium moving in the opposite direction (74).

Changes in plasma bicarbonate concentration, independent of the effect on extracellular pH, can reciprocally affect plasma potassium concentration (80). Movement of bicarbonate (outward at a low extracellular bicarbonate concentration and inward at a high extracellular bicarbonate concentration) between the intracellular and extracellular compartments may be causally related to a concomitant transfer of potassium. This relationship may account for the less marked increase in plasma potassium observed during acute respiratory acidosis, a condition characterized by an acid plasma pH with an elevated serum bicarbonate (leading to inward net bicarbonate and potassium movement), as compared with acute metabolic acidosis with a low serum bicarbonate concentration (leading to outward net bicarbonate and potassium movement). Though recommended as a mainstay of therapy, alkalinization of the extracellular fluid with sodium bicarbonate to promote the rapid cellular uptake of potassium may not be useful in patients on maintenance hemodialysis for end stage renal disease (61) (*Fig. 8-2*). However, this maneuver remains valuable if metabolic acidosis is at all responsible for the hyperkalemia. The major toxicities of bicarbonate therapy include sodium overload and precipitation of tetany in the face of preexisting hypocalcemia.

Other Factors

A number of other pathologic perturbations alter the internal potassium balance. An increase in plasma osmolality secondary to severe dehydration or administration of osmotically active agents causes water to shift out of cells. The consequent increase in intracellular potassium concentration exaggerates the transcellular concentration gradient and favors movement of this cation out of cells. The effect of hyperosmolality on potassium balance becomes especially problematic in diabetic patients with hyperglycemia, in whom the absence of insulin exacerbates the hyperkalemia.

Succinylcholine, a depolarizing paralytic agent and an agonist of nicotinic acetylcholine receptors, which are found predominantly in skeletal myocyte membranes, may lead to efflux of potassium from myocytes into the extracellular fluid under certain pathologic states associated with upregulation and redistribution of the receptors, including states characterized by physical or chemical upper or lower motor neuron denervation, immobilization, infection, muscle trauma or inflammation and burn injury (81, 82).

Finally, parenteral administration of cationic amino acids such as lysine, arginine or epsilon-amino caproic acid (used to improve hemostasis in patients undergoing cardiac surgery) may lead to electroneutral exchange of cell potassium for the cationic amino acid in skeletal myocytes (83–85).

Regulation of External Potassium Balance

Renal Contribution

The kidney is the major excretory organ for potassium. In the adult, urinary potassium excretion generally parallels dietary intake. However, the renal adaptation to variations in dietary intake is rather sluggish. Extreme adjustments in the rate of renal potassium conservation cannot be achieved as rapidly as for sodium, nor are the adjustments as complete; whereas urinary sodium can be virtually eliminated within 3–4 days of sodium restriction, there is a minimum urinary potassium loss of about 10 mEq/day in the adult, even after several weeks of severe potassium restriction (86). An increase in dietary potassium intake is matched by a parallel increase in renal potassium excretion within hours, yet maximal rates of potassium excretion are not attained for several days after increasing potassium intake. In adults, renal potassium excretion follows a circadian rhythm, presumably determined by hypothalamic oscillators, and it is characterized by maximum output during times of peak activity (87). It is unknown whether a circadian cycle of urinary potassium excretion prevails in infancy.

Children and adults ingesting an average American diet that contains sodium in excess of potassium excrete urine with a sodium-to-potassium ratio greater than one (16, 88). Although breast milk and commercially available infant formulas generally provide a sodium-to-potassium ratio of approximately 0.5–0.6, the urinary sodium-to-potassium ratio in the newborn up to 4 months of age generally exceeds 1. This high ratio may reflect the greater requirement of potassium over sodium for growth. In fact, some premature (<34 weeks GA) newborns may excrete urine with a sodium-to-potassium ratio greater than 2, a finding suggesting significant salt wasting and a relative hyporesponsiveness of the neonatal kidney to mineralocorticoid activity (16).

Net urinary potassium excretion in the fully differentiated kidney reflects the sum of three processes:

glomerular filtration, reabsorption along the proximal tubule and the loop of Henle, and bidirectional transport (secretion and reabsorption) in the distal nephron (8, 89). Most of the factors known to modulate potassium excretion do so by altering the rate of potassium secretion.

Renal potassium clearance is low in newborns, even when it is corrected for their low glomerular filtration rate (16, 17). Infants, like adults, can excrete potassium at a rate that exceeds its glomerular filtration, reflecting the capacity for net tubular secretion. However, they are unable to excrete an exogenously administered potassium load as efficiently as the adult (90); specifically, the rate of potassium excretion normalized to body weight or kidney weight is less in newborn than older animals (91, 92). Comparison of the fractional delivery of potassium to the early distal tubule with that present in the final urine reveals that the distal nephron of the young (2-week-old) rat secretes approximately fivefold less potassium than the older (5-week-old) rat (93). Similarly, clearance studies in saline-expanded dogs also provide indirect evidence of a diminished secretory and enhanced reabsorptive capacity of the distal nephron to potassium early in life (94). Furthermore, premature neonates studied weekly after birth exhibited a 50% reduction in the fractional excretion of potassium between 26 and 30 weeks GA, in the absence of significant change in absolute urinary potassium excretion (15). To the extent that the filtered load of potassium increased almost threefold during this same time interval, the constancy of renal potassium excretion could be best explained by a developmental increase in the capacity of the kidney for potassium reabsorption (15). Please note that, in general, the limited potassium secretory capacity of the immature kidney becomes clinically relevant only under conditions of potassium excess.

Sites of Potassium Transport along the Nephron

Proximal Tubule

Potassium is freely filtered at the glomerulus. Thus, the concentration of potassium entering the proximal convoluted tubule (PCT) is similar to that of plasma. Approximately 65% of the filtered load of potassium is reabsorbed along the initial two-thirds of the proximal tubule, a fractional rate of reabsorption similar to that of sodium and water (95–97) (*Fig. 8-3*). A similar fraction (50–60%) of the filtered load of potassium is reabsorbed along the proximal tubules of suckling (13–15 days old) rats (93, 99).

Reabsorption of potassium along the early proximal tubule is passive, closely following that of sodium and water (100), and has been proposed to occur via solvent drag via the paracellular pathway and diffusion (101–103). Solvent drag depends on active sodium reabsorption, which generates local hypertonicity in the paracellular compartment, providing an osmotic force driving water reabsorption that entrains potassium in the reabsorbate. Potassium diffusion is driven by the lumen-positive transepithelial voltage in the second half of the proximal tubule, and the slightly elevated concentrations of potassium in the lumen (104).

In the proximal tubule, as in all other nephron segments discussed below, transepithelial sodium reabsorption requires the coordinated function of apical sodium transport proteins and the basolateral Na-K-ATPase which actively extrudes intracellular sodium into the interstitium, and thereby maintains the low intracellular sodium concentration and steep sodium concentration gradient critical to the driving force for apical sodium entry (*Fig. 8-3*). There is no evidence for specific regulation of potassium reabsorption along the proximal tubule, and most observed modulation of proximal reabsorption of this cation can be accounted for by alterations in sodium transport.

Electrogenic sodium-coupled entry of substrates such as amino acids and glucose across the luminal cell membrane of the proximal tubule as well as bicarbonate exit across the basolateral cell membrane are driven by the potential differences across the respective cell membranes, which are maintained by potassium flux through potassium channels (105). Electrophysiological studies in isolated perfused proximal tubules suggest that potassium movement from the cell to lumen maintains the electrical driving force for sodium-coupled cotransport in the proximal tubule. Immunohistochemical studies reveal that KCNE1 and KCNQ1, which together constitute the slowly activated component of the delayed rectifying potassium current in heart, also colocalize in the luminal membrane of the proximal tubule in mouse kidney, as does the cyclic nucleotide-gated, voltage-activated potassium channel KCNA10 (106, 107). The observation that KCNE1 knock-out mice exhibit an increased fractional excretion of fluid (with accompanying volume depletion), sodium, chloride, and glucose compared to their wild type littermates supports the critical role of KCNE1 in repolarizing the membrane potential in proximal tubule in response to sodium-coupled transport (107).

Notably, mutations in KCNQ1 give rise to the long QT syndrome (108).

Thick Ascending Limb of the Loop of Henle (TALH)

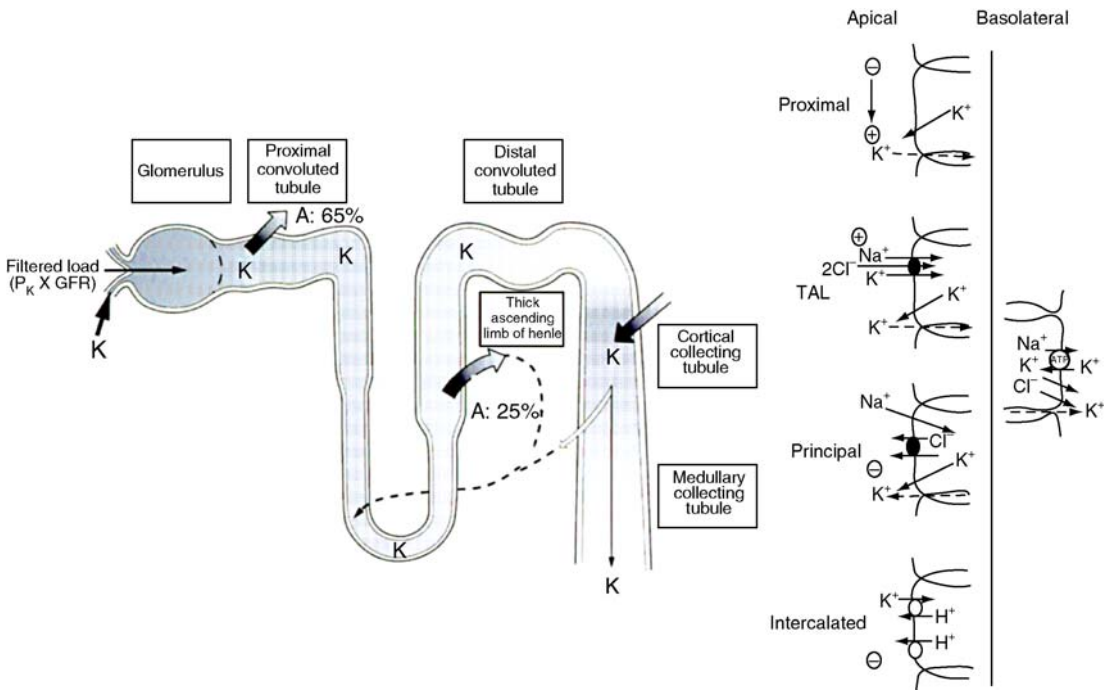
Approximately 10% of the filtered load of potassium reaches the early distal tubule of the adult rat (96), an observation that implies that significant reabsorption of this cation occurs beyond the proximal tubules. The site responsible for this additional avid potassium reabsorption is the TALH where potassium reabsorption is mediated, at least in part, by the apical Na-K-2Cl cotransporter (NKCC2) that translocates a single potassium ion into the cell accompanied by one sodium and two chloride ions (*Fig. 8-3*). This secondary active transport is ultimately driven by the low intracellular sodium concentration, established by the basolateral Na-K-ATPase, which drives sodium entry from the lumen into the cell. The diuretics furosemide and bumetanide specifically inhibit NKCC2 and thus block sodium, potassium and chloride reabsorption at this site.

Critical to the function of NKCC2 is the presence of a secretory potassium channel in the urinary membrane which provides a pathway for potassium, taken up into the cell via the cotransporter, to recycle back into the lumen. This "recycling" of potassium ensures that a continuous supply of substrate is available for the apical cotransporter. Potassium secretion into the urinary space creates a lumen positive transepithelial potential difference, which in turn provides a favorable electrical driving force that facilitates paracellular reabsorption of sodium, potassium, calcium and magnesium.

The luminal potassium secretory channel in the TALH has been identified as ROMK, a channel originally cloned from the TALH in the rat outer medulla (109–111); this low-conductance ATP-sensitive potassium channel is encoded by the KCNJ1 gene. Loss-of-function mutations in ROMK lead to antenatal Bartter syndrome (type 2),

Figure 8-3

Potassium transport along the nephron. (left panel) The percentages of filtered potassium reabsorbed along the proximal tubule and thick ascending limb of the loop of Henle (TALH) are indicated for the adult (A). *Arrows* show direction of net potassium transport (reabsorption or secretion). GFR = glomerular filtration rate. (right panel) Simplified cell models of potassium transport along the nephron, showing apical transporters unique to discrete nephron segments and cells therein, and basolateral transporters which are similar in all nephron segments (adapted from 98).



also known as the hyperprostaglandin E syndrome, which is characterized by severe renal salt and fluid wasting, electrolyte abnormalities (hypokalemia, hypomagnesemia, and hypercalciuria), and elevated renin and aldosterone levels (112). The clinical picture observed is similar to that of chronic administration of loop diuretics. The typical presentation of antenatal Bartter syndrome includes polyhydramnios, premature delivery, life threatening episodes of dehydration during the first week of life, and profound growth failure (113). It should be noted that mutations in NKCC2 (SLC12A1) or the basolateral chloride channel CLC-Kb (CLCNKB) can also give rise to Bartter syndromes type 1 and 3, respectively (114, 115).

In contrast to the situation in the adult, up to 35% of the filtered load of potassium reaches the early distal tubule of the young (2-week-old) rat (93), suggesting that the TALH undergoes a significant postnatal increase in its capacity for reabsorption. Consistent with this premise are the observations from studies in rats of significant increases in the (i) fractional reabsorption of potassium along the TALH, expressed as a percentage of delivered load, between the second and sixth weeks of postnatal life (93), and (ii) osmolarity of early distal fluid between the second and fourth weeks of life (116). While these findings provide compelling evidence for a developmental maturation of potassium absorptive pathways and diluting capacity of the TALH, respectively, direct functional analysis of the transport capacity of this segment in the developing nephron has not been performed.

Molecular studies in rat kidney indicate that mRNA encoding NKCC2, absent at birth, is first expressed on postnatal day 8 in rat, coincident with completion of nephronogenesis (37), and increases, at least in medulla, between postnatal days 10 and 40 (117). Na-K-ATPase activity in the TALH of the neonatal rabbit is only 20% of that measured in the adult when expressed per unit of dry weight (118). The postnatal increase in pump activity is associated with a parallel increase in expression of medullary Na-K-ATPase mRNA (117). Although the balance of the studies summarized above identifies a functional immaturity of the TALH early in life and would thus predict limited effects of inhibitors of NKCC2 on transepithelial transport, administration of furosemide (2 mg/kg) to newborn lambs leads to a natriuretic response equivalent to that observed in adult animals (119).

Distal Nephron

Within the distal nephron of the fully differentiated kidney, the late DCT, CNT and the CCD are considered to be the primary sites of potassium secretion, and thus urinary potassium excretion, which can approach 20% of the filtered load (96, 97, 120, 121) (*Fig. 8-3*). The DCT secretes a constant small amount of potassium into the urinary fluid (122). Regulated bidirectional potassium transport occurs in the CNT and CCD, comprised of two major populations of cells, each with distinct functional and morphologic characteristics. CNT/principal cells reabsorb sodium and secrete potassium, whereas intercalated cells regulate acid-base balance but can reabsorb potassium in response to dietary potassium restriction or metabolic acidosis (123, 124) (*Fig. 8-3*). Thus, the direction and magnitude of net potassium transport in these segments depend on the metabolic needs of the organism and reflect balance of potassium secretion and absorption, processes mediated by CNT/principal and intercalated cells, respectively.

Potassium Secretion

Potassium secretion in the CNT and CCD is critically dependent on the reabsorption of filtered sodium delivered to these segments. Sodium passively diffuses into the CNT/principal cell from the urinary fluid down a favorable concentration gradient through the luminal amiloride-sensitive epithelial Na channel (ENaC) and is then transported out of the cell at the basolateral membrane in exchange for the uptake of potassium via the basolateral Na-K-ATPase (*Fig. 8-3*). The accumulation of potassium within the cell and the lumen-negative voltage, created by movement of sodium from the tubular lumen into the cell and its electrogenic extrusion, creates a favorable electrochemical gradient for intracellular potassium to diffuse into the urinary space through apical potassium-selective channels. The magnitude of potassium secretion is determined by its electrochemical gradient and the apical permeability to this cation. Basolateral potassium channels in these same cells provide a route for intracellular potassium ions to recycle back into the interstitium, thereby maintaining the efficiency of the Na-K pump. Any factor that increases the electrochemical gradient across the apical membrane or increases the apical potassium permeability will promote potassium secretion. An apical electroneutral potassium-chloride cotransporter has also been functionally identified in the CCD (125, 126).

Two apical potassium-selective channels have been functionally identified in the distal nephron: the small-conductance secretory potassium (SK) channel and the high-conductance maxi-K channel. The density of these channels appears to be greater in the CNT than in the CCD (127).

The SK channel, restricted to the CNT/principal cell, mediates baseline potassium secretion (128, 129). ROMK, originally cloned from the TALH (described in the section above on the TALH), is considered to be a major functional subunit of the SK channel. A complex interplay of hormones, second messengers and kinases/phosphatases regulate the SK/ROMK channel in the distal nephron, thereby allowing the kidney to respond appropriately to the metabolic needs of the organism (130, 131). Protein kinase A (PKA)-induced phosphorylation of the channel is essential for its activity (129, 132), and may account for the well-documented stimulatory effect of vasopressin on renal potassium secretion (133). Protein tyrosine kinase (PTK) mediates the endocytosis of ROMK channels in the rat CCD in the face of dietary potassium restriction (134, 135). Tyrosine phosphorylation of ROMK enhances channel internalization and thus the removal of channels from the plasma membrane (136), leading to a reduction in number of apical channels and net potassium secretion. Tyrosine phosphorylation of ROMK channels decreases in response to dietary potassium loading (137).

The "with-no-lysine-kinases," or WNKs, comprise a recently discovered family of serine/threonine kinases that act as molecular switches that direct differential effects on downstream ion channels, transporters, and the paracellular pathway to allow either maximal sodium chloride reabsorption or maximal potassium secretion in response to hypovolemia or hyperkalemia, respectively (138). WNK4 inhibits sodium and chloride absorption in the DCT by reducing the surface expression of the apical thiazide-sensitive NaCl cotransporter NCCT (139), an effect that would be expected to increase sodium delivery to and reabsorption by the CCD, in turn augmenting the driving force for potassium secretion. However, WNK4 decreases surface expression of ROMK by enhancing endocytosis of this channel (140), thereby negating the effect of the augmented electrochemical gradient on stimulation of net potassium secretion. Mutations in WNK1 or 4 lead to pseudohypoaldosteronism type II (PHA II; Gordon's Syndrome), an autosomal dominant disorder characterized by hypertension sensitive to thiazide diuretics, hyperkalemia, and metabolic acidosis (141). Loss-of-function mutations in WNK4 lead to increased apical expression of the NaCl cotransporter and stimulation of sodium absorption in the DCT (139, 142). The consequent reduction in sodium delivery to the CNT and CCD would be expected to reduce potassium secretion. However, the same mutations in WNK4 that relieve the inhibition of NCCT further decrease surface expression of ROMK, reduce potassium secretion in the CCD, and likely are the cause of hyperkalemia in patients with Gordon's Syndrome. WNK1 suppresses the activity of WNK4. Therefore, a gain-in-function mutation in WNK1 will also produce the clinical signs and symptoms of PHA II (141).

The maxi-K channel, present in CNT/principal and intercalated cells, is considered to mediate flow-stimulated potassium secretion (143, 144). In the CNT and CCD, the density of conducting maxi-K channels is greater in intercalated than CNT/principal cells (145, 146). The maxi-K channel is comprised of two subunits: a channel pore-forming α subunit and a regulatory β subunit. This channel is rarely open at the physiologic resting membrane potential, but can be activated by cell depolarization, membrane stretch, and increases in intracellular Ca^{2+} concentration, as accompany increases in urinary flow rate (146–149). The proposed role of the maxi-K channel in flow-stimulated urinary potassium secretion has been confirmed in a mouse model with targeted deletion of the β1 subunit; the fractional excretion of potassium in maxi-K $\beta1^{-/-}$ mice subjected to acute volume expansion was significantly lower than that in wild type mice (150).

The maxi-K channel appears to assume great importance in regulating potassium homeostasis under conditions where SK/ROMK channel-mediated potassium secretion is limited. Thus, adult animals with targeted deletion of ROMK (i.e., Bartter phenotype) are not hyperkalemic, as would be expected in the absence of a primary potassium secretory channel, but instead lose urinary potassium (151). The sensitivity of distal potassium secretion in this rodent model of Bartter syndrome to iberiotoxin, a specific inhibitor of maxi-K channels, presumably reflects recruitment of the latter channels to secrete potassium in response to high distal flow rates as accompany loss-of-function of the TALH NKCC2 cotransporter (151). Similarly, although infants with antenatal Bartter syndrome due to loss-of-function mutations in ROMK may exhibit severe hyperkalemia during the first few days of life (152), the hyperkalemia is not sustained. In fact, these patients typically exhibit modest hypokalemia beyond the neonatal period (153, 154).

Potassium Absorption

In response to dietary potassium restriction or metabolic acidosis, the distal nephron may reverse the direction of net potassium transport from secretion to absorption. Potassium reabsorption is mediated by a H-K-ATPase, localized to the apical membrane of acid-base transporting intercalated cells, that couples potassium reabsorption to proton secretion (*Fig. 8-3*) (123, 155–157). Two isoforms of the H-K-ATPase are found in the kidney: the gastric isoform, HKAg, is normally found in gastric parietal cells and is responsible for acid secretion into the

lumen whereas the colonic HKAc isoform is a structurally related H-K-ATPase found in distal colon that mediates active potassium reabsorption (156). Expression of the apical gastric-like H-K-ATPase in the rat and rabbit intercalated cell is increased in response to dietary potassium restriction and metabolic acidosis (123, 155, 158, 159).

A reduction in potassium intake leads to a fall in potassium secretion by the distal nephron within 5–7 days in rat (160). This adaptation is associated with a decrease in the number of apical SK/ROMK (161) and maxi-K (162) channels and stimulation of H-K-ATPase-mediated potassium reabsorption in intercalated cells in the distal nephron (163). The reduction in number of SK/ROMK channels in potassium-restricted animals is mediated by the effect of dietary potassium on circulating levels of aldosterone and other effectors, such as PTK, as described above. Stimulation of luminal H-K-ATPase activity in intercalated cells results not only in potassium retention, but also in urinary acidification and metabolic alkalosis.

Developmental Regulation of Distal Potassium Transport

Potassium secretion in the distal nephron, and specifically in the cortical collecting duct (CCD) studied in vitro, is low early in life and cannot be stimulated by high urinary flow rates (121). Indeed, basal potassium secretion can not be detected in the rabbit CCD until after the third week of postnatal life, with potassium secretory rates increasing thereafter to reach adult levels by 6 weeks of age (121). Consistent with the relatively undifferentiated state of the newborn CCD are the ultrastructural and morphometric findings in neonatal principal cells of few organelles, mitochondria and basolateral infoldings, the site of Na-K-ATPase (164, 165).

The limited capacity of the CCD for potassium secretion early in life could be explained by either an unfavorable electrochemical gradient across the apical membrane and/or a limited apical permeability to this ion. Cumulative evidence suggests that the electrochemical gradient is not limiting for potassium secretion in the neonate. Activity of the Na-K-ATPase, present along the basolateral membrane of corticomedullary collecting ducts in the neonatal rabbit (166), is 50% of that measured in the mature nephron; the observation that the intracellular potassium concentration in this segment is similar in the neonate and adult presumably reflects a relative paucity of membrane potassium channels in the distal nephron early in life (118, 165, 167). Concordant with the measurements of sodium pump activity, the rate of sodium absorption in the CCD at 2 weeks of age is approximately 60% of that measured in the adult (121). However, electrophysiologic analysis has confirmed the absence of functional SK/ROMK channels in the luminal membrane of the neonatal rabbit CCD with the number of open channels per patch increasing progressively after the second week of life (168). Thus, the postnatal increase in the basal potassium secretory capacity of the distal nephron appears to be due primarily to a developmental increase in number of SK/ROMK channels, reflecting an increase in transcription and translation of functional channel proteins (168–170).

The appearance of flow-stimulated net potassium secretion is a relatively late developmental event. Flow-stimulated potassium secretion can not be elicited in rabbit CCDs until the fifth week of postnatal life, which is approximately 2 weeks after basal net potassium secretion is first detected (121, 171). The absence of flow-stimulated potassium secretion early in life is not due to a limited flow-induced rise in net sodium absorption and/or intracellular calcium concentration, each of which is required for flow stimulation of potassium secretion and is equivalent to that detected in the adult by the second week of postnatal life (171). The observation that mRNA encoding the maxi-K channel α-subunit and immunodetectable channel protein can not be demonstrated until the fourth and fifth weeks of postnatal life, respectively (171) suggests that flow-dependent potassium secretion is determined by the transcriptional/translational regulation of expression of maxi-K channels.

While the neonatal distal nephron is limited in its capacity for potassium secretion, indirect evidences suggests that this nephron segment absorbs potassium. As indicated above, saline-expanded newborn dogs absorb 25% more of the distal potassium load than do their adult counterparts (91). Functional analysis of the rabbit collecting duct has shown that the activity of apical H-K-ATPase in neonatal intercalated cells is equivalent to that in mature cells (123). The latter data alone do not predict transepithelial potassium absorption under physiologic conditions, as the balance of transport will depend on the presence and activity of apical and basolateral potassium conductances and the potassium concentration of the tubular fluid delivered to this site. The high distal tubular fluid potassium concentrations, as measured In vivo in the young rat, may facilitate lumen-to-cell potassium absorption mediated by the H-K-ATPase (93).

Luminal and Peritubular Factors Affecting Potassium Transport

The major factors that influence the external balance of potassium are listed in *Table 8-2* and are discussed in the following sections.

Table 8-2

Factors that regulate external potassium balance

Renal factors
Distal sodium delivery and transepithelial voltage
Tubular (urinary) flow rate
Potassium intake/plasma potassium concentration
Hormones (mineralocorticoids, vasopressin)
Acid-base balance
Gastrointestinal tract factors
Stool volume
Hormones (mineralocorticoids)

Sodium Delivery and Absorption

The magnitude of sodium reabsorption in the distal nephron determines the electrochemical driving force favoring potassium secretion into the luminal fluid, as described above. Processes that enhance distal sodium delivery and increase tubular fluid flow rate, such as extracellular volume expansion or administration of a variety of diuretics (osmotic diuretics, carbonic anhydrase inhibitors, loop and thiazide diuretics), lead to an increase in urinary excretion of both sodium and potassium. The kaliuresis is due not only to the increased delivery of sodium to the distal nephron, but also to the increase in tubular fluid flow rate, which maximizes the chemical driving forces, as described below, favoring potassium secretion.

Processes that decrease sodium delivery to less than 30 mM in the distal tubular fluid (172, 173) and/or sodium reabsorption sharply reduce potassium secretion in the CCD and can lead to hyperkalemia. In vivo measurements of the sodium concentration in distal tubular fluid generally exceed 35 mEq/L both in healthy adult and suckling rats and thus should not restrict distal sodium secretion (93, 116, 172, 174). However, in edema-forming states, including congestive heart failure, cirrhosis and nephrotic syndrome, the urinary sodium concentration typically falls to less than 10 mEq/L; a reduction in potassium excretion in these patients may be ascribed to the low rates of distal sodium delivery as well as urinary flow. The potassium-sparing diuretics, amiloride and triamterene, inhibit ENaC and thus block sodium absorption, thereby diminishing the electrochemical gradient favoring potassium secretion (175). Trimethoprim and pentamidine can also limit urinary potassium secretion via the same mechanism (177, 178).

Sodium delivered to the distal nephron is generally accompanied by chloride. Chloride reabsorption occurs predominantly via the paracellular pathway. The movement of the negative charged chloride out of the lumen dissipates the lumen negative potential, creating a less favorable driving force for luminal potassium secretion (179). When sodium delivered to the distal nephron is accompanied by an anion less reabsorbable than chloride, such as bicarbonate (in proximal renal tubular acidosis), β-hydroxybutyrate (in diabetic ketoacidosis), or carbenicillin (during antibiotic therapy), luminal electronegativity is maintained, thereby eliciting more potassium secretion than occurs with a comparable sodium load delivered with chloride (180).

Tubular Flow Rate

High rates of urinary flow in the mature, but not the neonatal or weanling, distal nephron, as elicited by extracellular fluid volume expansion or administration of diuretics or osmotic agents, stimulate potassium secretion (121). There are a number of factors responsible for the flow-stimulation of potassium secretion. First, increases in tubular fluid flow rate in the distal nephron enhance sodium reabsorption due to an increase in the open probability of ENaC (time the channel spends in the open state), which augments the electrochemical gradient favoring potassium secretion (176, 181). Second, the higher the urinary flow rate in the distal nephron, the slower the rate of rise of tubular fluid potassium concentration because secreted potassium is rapidly diluted in urine of low potassium concentration (182). Maintenance of a low tubular fluid potassium concentration maximizes the potassium concentration gradient (and thus the chemical driving force) favoring net potassium secretion. Finally, increases in luminal flow rate transduce mechanical signals (circumferential stretch, shear stress, hydrodynamic bending moments on the cilium decorating the apical surface of virtually all renal epithelial cells) into increases in intracellular calcium concentration, which in turn activate apical maxi-K channels to secrete potassium, thereby enhancing urinary potassium excretion (143, 144, 171).

Potassium Intake and Cellular Potassium Content

The kidney adjusts potassium excretion to match input, in large part by regulating the magnitude of potassium secretion and reabsorption in the distal nephron. Thus, for example, an increase in dietary potassium intake

stimulates whereas a decrease in intake reduces net potassium secretion (97). An increase in potassium concentration in the extracellular fluid space increases potassium entry into principal cells via the basolateral Na-K-ATPase, which in turn maximizes the concentration gradient favoring apical potassium secretion into the urinary fluid. Simultaneously, the increase in circulating levels of plasma aldosterone that accompanies potassium loading enhances the electrochemical driving force favoring potassium secretion in the distal nephron by stimulation of ENaC-mediated sodium absorption and its electrogenic absorption via the Na-K-ATPase. Within 6 h of an increase in dietary potassium intake, the density of apical ROMK channels increases in principal cells in rats due to activation of a previously "silent" pool of channels or closely associated proteins (183). Chronic potassium loading also increases maxi-K channel message, apical protein, and function in the distal nephron (162). Finally, the inhibition of proximal tubule and loop of Henle salt and water reabsorption in response to a potassium load (184, 185) increases tubule fluid flow rate which in turn stimulates potassium secretion via activation of maxi-K channels and increased distal of delivery of sodium to the distal nephron.

The trigger for the renal adaptation to dietary potassium loading remains uncertain. It is now believed that after a potassium-rich meal, a reflex increase in potassium excretion is initiated by sensors in the splanchnic bed (gut, portal circulation, and/or liver) that respond to local increases in potassium concentration that occur in the absence of or before changes in plasma potassium concentration are detected (87, 186). In support of the notion of potassium sensing, intraportal delivery of potassium chloride to rats leads to an increase in hepatic afferent nerve activity and urinary potassium excretion, responses that are unaccompanied by increases in plasma potassium concentration (187). Increases in the intraportal concentration of glucagon, as follows ingestion of a protein- and potassium-rich meal, also increases renal excretion of potassium (188, 189), a response proposed to be due to the release of cAMP, the second messenger of glucagon in the liver, into the circulation and its uptake by kidney (186).

Chronic potassium loading leads to *potassium adaptation,* an acquired tolerance to an otherwise lethal acute potassium load (8). Potassium adaptation, which begins after a single potassium-rich meal, includes increases in the rate of skeletal muscle uptake of potassium from the extracellular fluid (53) due to stimulation of Na-K-ATPase activity (190) and secretion of potassium by the distal nephron and colon. The process is facilitated by the increase in circulating levels of aldosterone elicited by the increase in serum potassium concentration (191). A similar adaptive response is seen in renal insufficiency such that potassium balance is maintained during the course of many forms of progressive renal disease, as long as potassium intake is not excessive (192). The molecular mechanisms underlying this adaptation in the distal nephron (and colon) include not only an increase in the density of apical membrane potassium channels, but also an increase in the number of conducting ENaC channels and activity of the basolateral Na-K pump. The latter two processes result in increases in transepithelial voltage and the intracellular potassium concentration, events that enhance the driving force favoring potassium diffusion from the cell into the urinary fluid.

Hormones

Mineralocorticoids are key regulators of renal sodium absorption and potassium excretion, and thus of circulating volume, blood pressure and sodium and potassium homeostasis. The major stimuli for aldosterone release from the zona glomerulosa in the adrenal gland are angiotensin II and elevations in serum potassium concentrations (193). ACE inhibitors, by reducing the conversion of angiotensin I to angiotensin II and thus aldosterone secretion by the adrenal gland, may lead to hyperkalemia as the ability of the distal nephron to secrete potassium is impaired. Angiotensin receptor blockers (ARBs), by competitively binding to angiotensin II type 1 (AT1) receptors and thus antagonizing the action of angiotensin II on aldosterone release, may have similar effects.

Aldosterone stimulates sodium reabsorption and potassium secretion in principal cells of the fully differentiated aldosterone-sensitive distal nephron (ASDN) (194, 195). Circulating mineralocorticoids bind to their cytosolic receptors in the ASDN; the aldosterone antagonist spironolactone competitively inhibits this binding. The hormone-receptor complex translocates to the nucleus where it promotes the transcription of aldosterone-induced physiologically active proteins (e.g., Na-K-ATPase). Among the cellular and molecular effects of an increase in circulating levels of aldosterone are increases in density of ENaC channels, achieved by the recruitment to and retention of intracellular channels at the apical membrane, de novo synthesis of new ENaC subunits, and activation of preexistent channels, as well as and stimulation of Na-K-ATPase activity by translocation of preformed transporters to the membrane and translation of new sodium pump subunits (196–201). The sum effect of the stimulation of apical

sodium entry and Na-pump-mediated reabsorption is an increase in lumen negative transepithelial voltage and thus electrochemical driving force favoring potassium exit across the apical membrane (199, 200, 202).

The effects of aldosterone on ENaC and, to some extent, the Na-K pump appear to be indirect, mediated by aldosterone-induced proteins, including serum and glucocorticoid-inducible kinase (sgk). Aldosterone rapidly induces Sgk1 in the distal nephron (203). Phosphorylated Sgk stimulates sodium reabsorption, in large part by inhibiting ubiquitin-ligase Nedd4-2-mediated endocytic retrieval of ENaCs from the luminal membrane (204). Renal water and electrolyte excretion is indistinguishable in sgk1-knockout ($sgk1^{-/-}$) and wild-type ($sgk1^{+/+}$) mice fed a normal diet (205), indicating that the kinase is not necessary for basal sodium absorption. However, dietary sodium restriction reveals an impaired ability of $sgk1^{-/-}$ mice to reduce sodium excretion despite increases in plasma aldosterone levels and proximal tubular sodium and fluid reabsorption (206). $Sgk1^{-/-}$mice exhibit an impaired upregulation of renal potassium excretion in response to potassium loading, presumably due to the impact of the mutation on ENaC and/or Na-K-ATPase activity and thus the electrochemical gradient favoring potassium secretion (207). Corticosteroid hormone induced factor (CHIF) is another aldosterone-induced protein that is expressed in the basolateral membrane of the collecting duct where it increases the affinity of Na-K-ATPase for sodium (208–211).

Plasma aldosterone concentrations in premature infants and newborns are higher than those measured in the adult (16, 212). Yet, clearance studies in fetal and newborn animals demonstrate a relative insensitivity of the immature kidney to the hormone (16, 213–215). The density of aldosterone binding sites, receptor affinity, and degree of nuclear binding of hormone-receptor are believed to be similar in mature and immature rats (215).

The transtubular potassium gradient (TTKG) provides an indirect, semiquantitative measure of the renal response to mineralocorticoid activity in the aldosterone-sensitive cortical distal nephron and is calculated using the equation:

$$\text{TTKG} = \frac{[K^+]\text{urine}}{[K^+]\text{plasma}} \times \frac{\text{plasma osmolality}}{\text{urine osmolality}}$$

where $[K^+]$ equals the potassium concentration in either urine (U) or plasma (P), as indicated (216–218). Measurements of TTKG have been reported to be lower in 27 than 30-week GA preterm infants followed over the first 5 weeks of postnatal life (219). The low TTKG has been attributed to a state of relative hypoaldosteronism (219), but may also reflect the absence of potassium secretory transport pathways (i.e., channel proteins).

Acid-Base Balance

Disorders of acid-base homeostasis induce changes in tubular potassium secretion in the distal nephron (179). In general, acute metabolic acidosis causes the urine pH and potassium excretion to decrease, whereas both acute respiratory alkalosis and metabolic alkalosis increase urine pH and potassium excretion (179, 220). Chronic metabolic acidosis has variable effects on urinary potassium excretion.

Acute metabolic acidosis reduces cell potassium concentration and leads to a reduction in urine pH, which in turns inhibits activity of the SK/ROMK channel and thereby limits potassium secretion in the distal nephron (220–223). The effect of chronic metabolic acidosis on potassium secretion is more complex and may be influenced by modifications of the glomerular filtrate (e.g., chloride and bicarbonate concentrations), tubular fluid flow rate, and circulating aldosterone levels (8, 179). The latter two factors may lead to an increase rather than a decrease in potassium secretion and excretion.

The alkalosis-induced stimulation of potassium secretion reflects two direct effects on principal cells: an increase in net sodium absorption (224), which enhances the electrochemical gradient for net potassium secretion, and (74) an increase in the permeability of the apical membrane to potassium resulting from an increase in duration of time the potassium-selective channels remain open (8). Alkalosis also decreases acid secretion in intercalated cells, thereby reducing H-K-ATPase-mediated countertransport of potassium.

Potassium deficiency stimulates proton secretion in the distal nephron, increases the production of the urinary buffer ammonia (225), and may stimulate bicarbonate generation by increasing expression H-K-ATPase in the distal nephron (226).

Contribution of the Gastrointestinal Tract

Under normal conditions in the adult, 5–10% of daily potassium intake is excreted in the stool. The colon is considered to be the main target for regulation of intestinal potassium excretion (227). Potassium transport in the colon represents the balance of secretion and absorption (228). Under baseline conditions, net potassium secretion predominates over absorption in the adult, whereas the neonatal gut is poised for net potassium absorption (227).

Potassium secretion requires potassium uptake by the Na-K-ATPase and furosemide-sensitive Na-K-2Cl cotransporter located in the basolateral membrane of colonocytes; potassium is then secreted across the apical membrane through potassium channels, including a calcium-activated maxi-K channel similar to that found in the distal nephron (229–233). Potassium absorption is mediated by two H-K-ATPases localized to the apical membrane of the distal colon (234).

Stool potassium content can be enhanced by any factor that increases colonic secretion, including aldosterone, epinephrine, and prostaglandins (31, 235, 236). Indomethacin and dietary potassium restriction reduce potassium secretion by inhibiting the basolateral transporters and apical potassium channels. Diarrheal illnesses are typically associated with hypokalemia, presumably due to the presence of nonreabsorbed anions (which obligate potassium), an enhanced electrochemical gradient established by active chloride secretion, and secondary hyperaldosteronism due to volume contraction (237).

Potassium adaptation in the colon is demonstrated by increased fecal potassium secretion after potassium loading and in the face of renal insufficiency. Fecal potassium excretion may increase substantially to account for 30–50% of potassium excretion in patients with severe chronic renal insufficiency (31, 238–240). The enhanced colonic potassium secretion characteristic of renal insufficiency requires induction and/or activation of apical maxi-K channels in surface colonic epithelial cells (241).

Net colonic potassium absorption is significantly higher in young compared to adult rats (227). The higher rate of potassium absorption during infancy is due to robust activity of apical K-ATPases and limited activity of the basolateral transporters that mediate secretion (227, 231, 242).

References

1. Adler S, Fraley DS. Potassium and intracellular pH. *Kidney Int* 1977;11:433–442.
2. Bygrave FL. The ionic environment and metabolic control. *Nature* 1967;214:667–671.
3. Lang F, Foller M, Lang KS, Lang PA, Ritter M, Gulbins E, Vereninov A, Huber SM. Ion channels in cell proliferation and apoptotic cell death. *J Membr Biol* 2005;205:147–157.
4. Lopez-Rivas A, Adelberg EA, Rozengurt E. Intracellular K^+ and the mitogenic response of 3T3 cells to peptide factors in serum-free medium. *Proc Natl Acad Sci USA* 1982;79:6275–6279.
5. Lubin M. Intracellular potassium and macromolecular synthesis in mammalian cells. *Nature* 1967;213:451–453.
6. Schmidt-Nielsen B. Comparative physiology of cellular ion and volume regulation. *J Exp Zool* 1975;194:207–219.
7. Weiner MW, Sauer LA, Torretti J, Epstein FH. Renal mitochondrial enzymes in potassium depletion. *Am J Physiol* 1971;221:613–617.
8. Giebisch G. Renal potassium transport: mechanisms and regulation. *Am J Physiol* 1998;274:F817–F833.
9. Butte NF, Hopkinson JM, Wong WW, Smith EO, Ellis KJ. Body composition during the first 2 years of life: an updated reference. *Pediatr Res* 2000;47:578–585.
10. Flynn MA, Woodruff C, Clark J, Chase G. Total body potassium in normal children. *Pediatr Res* 1972;6:239–245.
11. Dickerson JW, Widdowson EM. Chemical changes in skeletal muscle during development. *Biochem J* 1960;74:247–257.
12. Rutledge MM, Clark J, Woodruff C, Krause G, Flynn MA. A longitudinal study of total body potassium in normal breastfed and bottle-fed infants. *Pediatr Res* 1976;10:114–117.
13. Dorup I, Clausen T. Effects of potassium deficiency on growth and protein synthesis in skeletal muscle and the heart of rats. *Br J Nutr* 1989;62:269–284.
14. Wilde WS. Potassium. New York, Academic Press, 1962, pp. 73–107.
15. Delgado MM, Rohatgi R, Khan S, Holzman IR, Satlin LM. Sodium and potassium clearances by the maturing kidney: clinical-molecular correlates. *Pediatr Nephrol* 2003;18:759–767.
16. Sulyok E, Nemeth M, Tenyi I, Csaba IF, Varga F, Gyory E, Thurzo V. Relationship between maturity, electrolyte balance and the function of the renin-angiotensin-aldosterone system in newborn infants. *Biol Neonate* 1979;35:60–65.
17. Satlin LM. Regulation of potassium transport in the maturing kidney. *Semin Nephrol* 1999;19:155–165.
18. Gruskay J, Costarino AT, Polin RA, Baumgart S. Nonoliguric hyperkalemia in the premature infant weighing less than 1000 grams. *J Pediatr* 1988;113:381–386.
19. Leslie GI, Carman G, Arnold JD. Early neonatal hyperkalaemia in the extremely premature newborn infant. *J Paediatr Child Health* 1990;26:58–61.
20. Lorenz JM, Kleinman LI, Markarian K. Potassium metabolism in extremely low birth weight infants in the first week of life. *J Pediatr* 1997;131:81–86.
21. Sato K, Kondo T, Iwao H, Honda S, Ueda K. Internal potassium shift in premature infants: cause of nonoliguric hyperkalemia. *J Pediatr* 1995;126:109–113.
22. Shaffer SG, Kilbride HW, Hayen LK, Meade VM, Warady BA. Hyperkalemia in very low birth weight infants. *J Pediatr* 1992;121:275–279.
23. Stefano JL, Norman ME, Morales MC, Goplerud JM, Mishra OP, Delivoria-Papadopoulos M. Decreased erythrocyte Na^+, K^+-ATPase activity associated with cellular potassium loss in extremely low birth weight infants with nonoliguric hyperkalemia. *J Pediatr* 1993;122:276–284.
24. Omar SA, DeCristofaro JD, Agarwal BI, LaGamma EF. Effect of prenatal steroids on potassium balance in extremely low birth weight neonates. *Pediatrics* 2000;106:561–567.
25. Uga N, Nemoto Y, Ishii T, Kawase Y, Arai H, Tada H. Antenatal steroid treatment prevents severe hyperkalemia in very low-birthweight infants. *Pediatr Int* 2003;45:656–660.
26. Mohammed T, Stulc J, Glazier JD, Boyd RD, Sibley CP. Mechanisms of potassium transfer across the dually perfused rat placenta. *Am J Physiol* 1993;265:R341–R347.
27. Serrano CV, Talbert LM, Welt LG. Potassium deficiency in the pregnant dog. *J Clin Invest* 1964;43:27–31.
28. Dancis J, Springer D. Fetal homeostasis in maternal malnutrition: potassium and sodium deficiency in rats. *Pediatr Res* 1970;4:345–351.

29. DeFronzo RA, Sherwin RS, Dillingham M, Hendler R, Tamborlane WV, Felig P. Influence of basal insulin and glucagon secretion on potassium and sodium metabolism. Studies with somatostatin in normal dogs and in normal and diabetic human beings. *J Clin Invest* 1978;61:472–479.
30. DeFronzo RA, Taufield PA, Black H, McPhedran P, Cooke CR. Impaired renal tubular potassium secretion in sickle cell disease. *Ann Intern Med* 1979;90:310–316.
31. Bia MJ, DeFronzo RA. Extrarenal potassium homeostasis. *Am J Physiol* 1981;240:F257–F268.
32. Geering K. The functional role of beta subunits in oligomeric P-type ATPases. *J Bioenerg Biomembr* 2001;33:425–438.
33. Benziane B, Chibalin AV. Frontiers: skeletal muscle sodium pump regulation: a translocation paradigm. *Am J Physiol Endocrinol Metab* 2008;295:E553–E558.
34. Clausen T. Na^+-K^+ pump regulation and skeletal muscle contractility. *Physiol Rev* 2003;83:1269–1324.
35. Therien AG, Blostein R. Mechanisms of sodium pump regulation. *Am J Physiol Cell Physiol* 2000;279:C541–C566.
36. Horster M. Embryonic epithelial membrane transporters. *Am J Physiol Renal Physiol* 2000;279:F982–F996.
37. Schmitt R, Ellison DH, Farman N, Rossier BC, Reilly RF, Reeves WB, Oberbaumer I, Tapp R, Bachmann S. Developmental expression of sodium entry pathways in rat nephron. *Am J Physiol* 1999;276: F367–F381.
38. McCaughan D. Hazards of non-prescription potassium supplements. *Lancet* 1984;1:513–514.
39. Zierler KL, Rabinowitz D. Effect of very small concentrations of insulin on forearm metabolism. Persistence of its action on potassium and free fatty acids without its effect on glucose. *J Clin Invest* 1964;43:950–962.
40. Hundal HS, Marette A, Mitsumoto Y, Ramlal T, Blostein R, Klip A. Insulin induces translocation of the alpha 2 and beta 1 subunits of the Na^+/K^+-ATPase from intracellular compartments to the plasma membrane in mammalian skeletal muscle. *J Biol Chem* 1992; 267:5040–5043.
41. Kanbe M, Kitasato H. Stimulation of Na, K-ATPase activity of frog skeletal muscle by insulin. *Biochem Biophys Res Commun* 1986; 134:609–616.
42. Lavoie L, Roy D, Ramlal T, Dombrowski L, Martin-Vasallo P, Marette A, Carpentier JL, Klip A. Insulin-induced translocation of Na^+-K^+-ATPase subunits to the plasma membrane is muscle fiber type specific. *Am J Physiol* 1996;270:C1421–C1429.
43. Marette A, Krischer J, Lavoie L, Ackerley C, Carpentier JL, Klip A. Insulin increases the Na^+-K^+-ATPase alpha 2-subunit in the surface of rat skeletal muscle: morphological evidence. *Am J Physiol* 1993;265:C1716–C1722.
44. Omatsu-Kanbe M, Kitasato H. Insulin stimulates the translocation of Na^+/K^+-dependent ATPase molecules from intracellular stores to the plasma membrane in frog skeletal muscle. *Biochem J* 1990;272:727–733.
45. Lytton J. Insulin affects the sodium affinity of the rat adipocyte (Na^+, K^+)-ATPase. *J Biol Chem* 1985;260:10075–10080.
46. Sargeant RJ, Liu Z, Klip A. Action of insulin on Na^+-K^+-ATPase and the Na^+-K^+-2Cl- cotransporter in 3T3-L1 adipocytes. *Am J Physiol* 1995;269:C217–C225.
47. Sweeney G, Klip A. Regulation of the Na^+/K^+-ATPase by insulin: why and how? *Mol Cell Biochem* 1998;182:121–133.
48. Feraille E, Carranza ML, Rousselot M, Favre H. Insulin enhances sodium sensitivity of Na-K-ATPase in isolated rat proximal convoluted tubule. *Am J Physiol* 1994;267:F55–F62.
49. Hiatt N, Davidson MB, Bonorris G. The effect of potassium chloride infusion on insulin secretion in vivo. *Horm Metab Res* 1972;4:64–68.
50. Pettit GW, Vick RL, Swander AM. Plasma K plus and insulin: changes during KCl infusion in normal and nephrectomized dogs. *Am J Physiol* 1975;228:107–109.
51. DeFronzo RA, Bia M, Birkhead G. Epinephrine and potassium homeostasis. *Kidney Int* 1981;20:83–91.
52. Brown RS. Extrarenal potassium homeostasis. *Kidney Int* 1986; 30:116–127.
53. Salem MM, Rosa RM, Batlle DC. Extrarenal potassium tolerance in chronic renal failure: implications for the treatment of acute hyperkalemia. *Am J Kidney Dis* 1991;18:421–440.
54. Todd EP, Vick RL. Kalemotropic effect of epinephrine: analysis with adrenergic agonists and antagonists. *Am J Physiol* 1971;220: 1964–1969.
55. Williams ME, Gervino EV, Rosa RM, Landsberg L, Young JB, Silva P, Epstein FH. Catecholamine modulation of rapid potassium shifts during exercise. *N Engl J Med* 1985;312:823–827.
56. Williams ME, Rosa RM, Silva P, Brown RS, Epstein FH. Impairment of extrarenal potassium disposal by alpha-adrenergic stimulation. *N Engl J Med* 1984;311:145–149.
57. Angelopoulous M, Leitz H, Lambert G, MacGilvray S. In vitro analysis of the Na^+-K^+ ATPase activity in neonatal and adult red blood cells. *Biol Neonate* 1996;69:140–145.
58. Clausen T, Flatman JA. The effect of catecholamines on Na-K transport and membrane potential in rat soleus muscle. *J Physiol* 1977;270:383–414.
59. Gillzan KM, Stewart AG. The role of potassium channels in the inhibitory effects of beta 2-adrenoceptor agonists on DNA synthesis in human cultured airway smooth muscle. *Pulm Pharmacol Ther* 1997;10:71–79.
60. Rosa RM, Silva P, Young JB, Landsberg L, Brown RS, Rowe JW, Epstein FH. Adrenergic modulation of extrarenal potassium disposal. *N Engl J Med* 1980;302:431–434.
61. Blumberg A, Weidmann P, Shaw S, Gnadinger M. Effect of various therapeutic approaches on plasma potassium and major regulating factors in terminal renal failure. *Am J Med* 1988;85:507–512.
62. Helfrich E, de Vries TW, van Roon EN. Salbutamol for hyperkalaemia in children. *Acta Paediatr* 2001;90:1213–1216.
63. Mandelberg A, Krupnik Z, Houri S, Smetana S, Gilad E, Matas Z, Priel IE. Salbutamol metered-dose inhaler with spacer for hyperkalemia: how fast? How safe? *Chest* 1999;115:617–622.
64. Singh BS, Sadiq HF, Noguchi A, Keenan WJ. Efficacy of albuterol inhalation in treatment of hyperkalemia in premature neonates. *J Pediatr* 2002;141:16–20.
65. Allon M. Hyperkalemia in end-stage renal disease: mechanisms and management. *J Am Soc Nephrol* 1995;6:1134–1142.
66. McClure RJ, Prasad VK, Brocklebank JT. Treatment of hyperkalaemia using intravenous and nebulised salbutamol. *Arch Dis Child* 1994;70:126–128.
67. Semmekrot BA, Monnens LA. A warning for the treatment of hyperkalaemia with salbutamol. *Eur J Pediatr* 1997;156:420.
68. Lui K, Thungappa U, Nair A, John E. Treatment with hypertonic dextrose and insulin in severe hyperkalaemia of immature infants. *Acta Paediatr* 1992;81:213–216.
69. Shortland D, Trounce JQ, Levene MI. Hyperkalaemia, cardiac arrhythmias, and cerebral lesions in high risk neonates. *Arch Dis Child* 1987;62:1139–1143.
70. Yeh TF, Raval D, John E, Pildes RS. Renal response to frusemide in preterm infants with respiratory distress syndrome during the first three postnatal days. *Arch Dis Child* 1985;60:621–626.

71. Lei J, Mariash CN, Bhargava M, Wattenberg EV, Ingbar DH. T3 increases Na-K-ATPase activity via a MAPK/ERK1/2-dependent pathway in rat adult alveolar epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 2008;294:L749–L754.
72. Lei J, Mariash CN, Ingbar DH. 3,3',5-Triiodo-L-thyronine up-regulation of Na, K-ATPase activity and cell surface expression in alveolar epithelial cells is Src kinase- and phosphoinositide 3-kinase-dependent. *J Biol Chem* 2004;279:47589–47600.
73. Nakhoul F, Thompson CB, McDonough AA. Developmental change in Na, K-ATPase alpha1 and beta1 expression in normal and hypothyroid rat renal cortex. *Am J Nephrol* 2000;20:225–231.
74. Adrogue HJ, Madias NE. Changes in plasma potassium concentration during acute acid-base disturbances. *Am J Med* 1981;71: 456–467.
75. Burnell JM, Scribner BH, Uyeno BT, Villamil MF. The effect in humans of extracellular pH change on the relationship between serum potassium concentration and intracellular potassium. *J Clin Invest* 1956;35:935–939.
76. Magner PO, Robinson L, Halperin RM, Zettle R, Halperin ML. The plasma potassium concentration in metabolic acidosis: a re-evaluation. *Am J Kidney Dis* 1988;11:220–224.
77. Oster JR, Perez GO, Vaamonde CA. Relationship between blood pH and potassium and phosphorus during acute metabolic acidosis. *Am J Physiol* 1978;235:F345–F351.
78. Fulop M. Serum potassium in lactic acidosis and ketoacidosis. *N Engl J Med* 1979;300:1087–1089.
79. Graber M. A model of the hyperkalemia produced by metabolic acidosis. *Am J Kidney Dis* 1993;22:436–444.
80. Fraley DS, Adler S. Correction of hyperkalemia by bicarbonate despite constant blood pH. *Kidney Int* 1977;12:354–360.
81. Cooperman LH. Succinylcholine-induced hyperkalemia in neuromuscular disease. *JAMA* 1970;213:1867–1871.
82. Martyn JA, Richtsfeld M. Succinylcholine-induced hyperkalemia in acquired pathologic states: etiologic factors and molecular mechanisms. *Anesthesiology* 2006;104:158–169.
83. Hertz P, Richardson JA. Arginine-induced hyperkalemia in renal failure patients. *Arch Intern Med* 1972;130:778–780.
84. Perazella MA, Biswas P. Acute hyperkalemia associated with intravenous epsilon-aminocaproic acid therapy. *Am J Kidney Dis* 1999;33:782–785.
85. Ponce SP, Jennings AE, Madias NE, Harrington JT. Drug-induced hyperkalemia. *Medicine (Baltimore)* 1985;64:357–370.
86. Ethier JH, Kamel KS, Magner PO, Lemann J, Jr., Halperin ML. The transtubular potassium concentration in patients with hypokalemia and hyperkalemia. *Am J Kidney Dis* 1990;15:309–315.
87. Rabinowitz L. Aldosterone and potassium homeostasis. *Kidney Int* 1996;49:1738–1742.
88. Rodriguez-Soriano J, Vallo A, Castillo G, Oliveros R. Renal handling of water and sodium in infancy and childhood: a study using clearance methods during hypotonic saline diuresis. *Kidney Int* 1981;20:700–704.
89. Gurkan S, Estilo GK, Wei Y, Satlin LM. Potassium transport in the maturing kidney. *Pediatr Nephrol* 2007;22:915–925.
90. Tudvad F, Mc NH, Barnett HL. Renal response of premature infants to administration of bicarbonate and potassium. *Pediatrics* 1954; 13:4–16.
91. Lorenz JM, Kleinman LI, Disney TA. Renal response of newborn dog to potassium loading. *Am J Physiol* 1986;251:F513–F519.
92. McCance R, Widdowson EM. The response of the new-born piglet to an excess of potassium. *J Physiol* 1958;141:88–96.
93. Lelievre-Pegorier M, Merlet-Benichou C, Roinel N, de Rouffignac C. Developmental pattern of water and electrolyte transport in rat superficial nephrons. *Am J Physiol* 1983;245:F15–F21.
94. Kleinman LI, Banks RO. Segmental nephron sodium and potassium reabsorption in newborn and adult dogs during saline expansion. *Proc Soc Exp Biol Med* 1983;173:231–237.
95. Malnic G, Klose RM, Giebisch G. Microperfusion study of distal tubular potassium and sodium transfer in rat kidney. *Am J Physiol* 1966;211:548–559.
96. Malnic G, Klose RM, Giebisch G. Micropuncture study of distal tubular potassium and sodium transport in rat nephron. *Am J Physiol* 1966;211:529–547.
97. Malnic G, Klose RM, Giebisch G. Micropuncture study of renal potassium excretion in the rat. *Am J Physiol* 1964;206:674–686.
98. Giebisch GH. A trail of research on potassium. *Kidney Int* 2002;62:1498–1512.
99. Solomon S. Absolute rates of sodium and potassium reabsorption by proximal tubule of immature rats. *Biol Neonate* 1974;25: 340–351.
100. Bomsztyk K, Wright FS. Dependence of ion fluxes on fluid transport by rat proximal tubule. *Am J Physiol* 1986;250:F680–F689.
101. Kibble JD, Wareing M, Wilson RW, Green R. Effect of barium on potassium diffusion across the proximal convoluted tubule of the anesthetized rat. *Am J Physiol* 1995;268:F778–F783.
102. Weinstein AM. Modeling the proximal tubule: complications of the paracellular pathway. *Am J Physiol* 1988;254:F297–F305.
103. Wilson RW, Wareing M, Green R. The role of active transport in potassium reabsorption in the proximal convoluted tubule of the anaesthetized rat. *J Physiol* 1997;500(Pt 1): 155–164.
104. Fromter E, Gessner K. Free-flow potential profile along rat kidney proximal tubule. *Pflugers Arch* 1974;351:69–83.
105. Edelman A, Curci S, Samarzija I, Fromter E. Determination of intracellular K^+ activity in rat kidney proximal tubular cells. *Pflugers Arch* 1978;378:37–45.
106. Yao X, Tian S, Chan HY, Biemesderfer D, Desir GV. Expression of KCNA10, a voltage-gated K channel, in glomerular endothelium and at the apical membrane of the renal proximal tubule. *J Am Soc Nephrol* 2002;13:2831–2839.
107. Vallon V, Grahammer F, Richter K, Bleich M, Lang F, Barhanin J, Volkl H, Warth R. Role of KCNE1-dependent K^+ fluxes in mouse proximal tubule. *J Am Soc Nephrol* 2001;12:2003–2011.
108. Wang Q, Curran ME, Splawski I, Burn TC, Millholland JM, VanRaay TJ, Shen J, Timothy KW, Vincent GM, de Jager T, Schwartz PJ, Toubin JA, Moss AJ, Atkinson DL, Landes GM, Connors TD, Keating MT. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. *Nat Genet* 1996;12:17–23.
109. Boim MA, Ho K, Shuck ME, Bienkowski MJ, Block JH, Slightom JL, Yang Y, Brenner BM, Hebert SC. ROMK inwardly rectifying ATP-sensitive K^+ channel. II. Cloning and distribution of alternative forms. *Am J Physiol* 1995;268:F1132–1140.
110. Ho K, Nichols CG, Lederer WJ, Lytton J, Vassilev PM, Kanazirska MV, Hebert SC. Cloning and expression of an inwardly rectifying ATP-regulated potassium channel. *Nature* 1993;362:31–38.
111. Zhou H, Tate SS, Palmer LG. Primary structure and functional properties of an epithelial K channel. *Am J Physiol* 1994;266: C809–C824.
112. International Collaborative Study Group for Bartter-like Syndromes, Konrad M, Köckerling A, Ziegler A, Zimmermann DK, Roth B, Wieg C, Grzeschik K-H, Koch MC, Seyberth HW, Group 2: Vargas R,

Forestier L, Jean G, Deschaux M, Rizzoni GF, Niaudet P, Antignac C, Group 3: Feldmann D, Lorridon F, Cougoureux E, Laroze F, Alessandri J-L, David L, Saunier P, Deschenes G, Group 4: Hildebrandt F, Vollmer M, Proesmans W, Brandis M, Group 5: van den Heuvel LP, Lemmink HH, Nillesen W, Monnens LAH, Knoers NVAM, Group 6: Guay-Woodford LM, Wright CJ, Madrigal G, Hebert SC. Mutations in the gene encoding the inwardly-rectifying renal potassium channel, ROMK, cause the antenatal variant of Bartter syndrome: evidence for genetic heterogeneity. International Collaborative Study Group for Bartter-like Syndromes. *Hum Mol Genet* 1997;6:17–26.

113. Simon DB, Lifton RP. The molecular basis of inherited hypokalemic alkalosis: Bartter's and Gitelman's syndromes. *Am J Physiol* 1996;271:F961–F966.
114. Simon DB, Bindra RS, Mansfield TA, Nelson-Williams C, Mendonca E, Stone R, Schurman S, Nayir A, Alpay H, Bakkaloglu A, Rodriguez-Soriano J, Morales JM, Sanjad SA, Taylor CM, Pilz D, Brem A, Trachtman H, Griswold W, Richard GA, John E, Lifton RP. Mutations in the chloride channel gene, CLCNKB, cause Bartter's syndrome type III. *Nat Genet* 1997;17:171–178.
115. Simon DB, Karet FE, Hamdan JM, DiPietro A, Sanjad SA, Lifton RP. Bartter's syndrome, hypokalaemic alkalosis with hypercalciuria, is caused by mutations in the Na-K-2Cl cotransporter NKCC2. *Nat Genet* 1996;13:183–188.
116. Zink H, Horster M. Maturation of diluting capacity in loop of Henle of rat superficial nephrons. *Am J Physiol* 1977;233:F519–F524.
117. Yasui M, Marples D, Belusa R, Eklof AC, Celsi G, Nielsen S, Aperia A. Development of urinary concentrating capacity: role of aquaporin-2. *Am J Physiol* 1996;271:F461–F468.
118. Schmidt U, Horster M. Na-K-activated ATPase: activity maturation in rabbit nephron segments dissected in vitro. *Am J Physiol* 1977;233:F55–F60.
119. Smith FG, Abraham J. Renal and renin responses to furosemide in conscious lambs during postnatal maturation. *Can J Physiol Pharmacol* 1995;73:107–112.
120. Imai M, Nakamura R. Function of distal convoluted and connecting tubules studied by isolated nephron fragments. *Kidney Int* 1982;22:465–472.
121. Satlin LM. Postnatal maturation of potassium transport in rabbit cortical collecting duct. *Am J Physiol* 1994;266:F57–F65.
122. Schnermann J, Steipe B, Briggs JP. In situ studies of distal convoluted tubule in rat. II. K secretion. *Am J Physiol* 1987;252:F970–F976.
123. Constantinescu A, Silver RB, Satlin LM. H-K-ATPase activity in PNA-binding intercalated cells of newborn rabbit cortical collecting duct. *Am J Physiol* 1997;272:F167–F177.
124. Satlin LM, Matsumoto T, Schwartz GJ. Postnatal maturation of rabbit renal collecting duct. III. Peanut lectin-binding intercalated cells. *Am J Physiol* 1992;262:F199–F208.
125. Velazquez H, Ellison DH, Wright FS. Chloride-dependent potassium secretion in early and late renal distal tubules. *Am J Physiol* 1987;253:F555–F562.
126. Wingo CS. Reversible chloride-dependent potassium flux across the rabbit cortical collecting tubule. *Am J Physiol* 1989;256:F697–F704.
127. Frindt G, Palmer LG. Apical potassium channels in the rat connecting tubule. *Am J Physiol Renal Physiol* 2004;287:F1030–F1037.
128. Frindt G, Palmer LG. Low-conductance K channels in apical membrane of rat cortical collecting tubule. *Am J Physiol* 1989;256:F143–F151.
129. Wang WH, Giebisch G. Dual modulation of renal ATP-sensitive K^+ channel by protein kinases A and C. *Proc Natl Acad Sci USA* 1991;88:9722–9725.
130. Wang WH. Regulation of ROMK (Kir1.1) channels: new mechanisms and aspects. *Am J Physiol Renal Physiol* 2006;290:F14–F19.
131. Wang WH, Giebisch G. Regulation of potassium (K) handling in the renal collecting duct. *Pflugers Arch* 2009;458:157–168.
132. Xu ZC, Yang Y, Hebert SC. Phosphorylation of the ATP-sensitive, inwardly rectifying K^+ channel, ROMK, by cyclic AMP-dependent protein kinase. *J Biol Chem* 1996;271:9313–9319.
133. Schafer JA, Troutman SL. Effect of ADH on rubidium transport in isolated perfused rat cortical collecting tubules. *Am J Physiol* 1986;250:F1063–F1072.
134. Lin DH, Sterling H, Wang WH. The protein tyrosine kinase-dependent pathway mediates the effect of K intake on renal K secretion. *Physiology (Bethesda)* 2005;20:140–146.
135. Lin DH, Sterling H, Yang B, Hebert SC, Giebisch G, Wang WH. Protein tyrosine kinase is expressed and regulates ROMK1 location in the cortical collecting duct. *Am J Physiol Renal Physiol* 2004;286:F881–F892.
136. Zeng WZ, Babich V, Ortega B, Quigley R, White SJ, Welling PA, Huang CL. Evidence for endocytosis of ROMK potassium channel via clathrin-coated vesicles. *Am J Physiol Renal Physiol* 2002;283:F630–F639.
137. Wang W. Regulation of renal K transport by dietary K intake. *Annu Rev Physiol* 2004;66:547–569.
138. Kahle KT, Ring AM, Lifton RP. Molecular physiology of the WNK kinases. *Annu Rev Physiol* 2008;70:329–355.
139. Wilson FH, Kahle KT, Sabath E, Lalioti MD, Rapson AK, Hoover RS, Hebert SC, Gamba G, Lifton RP. Molecular pathogenesis of inherited hypertension with hyperkalemia: the Na-Cl cotransporter is inhibited by wild-type but not mutant WNK4. *Proc Natl Acad Sci USA* 2003;100:680–684.
140. Kahle KT, Wilson FH, Leng Q, Lalioti MD, O'Connell AD, Dong K, Rapson AK, MacGregor GG, Giebisch G, Hebert SC, Lifton RP. WNK4 regulates the balance between renal NaCl reabsorption and K^+ secretion. *Nat Genet* 2003;35:372–376.
141. Wilson FH, Disse-Nicodeme S, Choate KA, Ishikawa K, Nelson-Williams C, Desitter I, Gunel M, Milford DV, Lipkin GW, Achard JM, Feely MP, Dussol B, Berland Y, Unwin RJ, Mayan H, Simon DB, Farfel Z, Jeunemaitre X, Lifton RP. Human hypertension caused by mutations in WNK kinases. *Science* 2001;293:1107–1112.
142. Xie J, Craig L, Cobb MH, Huang CL. Role of with-no-lysine [K] kinases in the pathogenesis of Gordon's syndrome. *Pediatr Nephrol* 2006;21:1231–1236.
143. Liu W, Morimoto T, Woda C, Kleyman TR, Satlin LM. Ca^{2+} dependence of flow-stimulated K secretion in the mammalian cortical collecting duct. *Am J Physiol Renal Physiol* 2007;293:F227–F235.
144. Woda CB, Bragin A, Kleyman TR, Satlin LM. Flow-dependent K^+ secretion in the cortical collecting duct is mediated by a maxi-K channel. *Am J Physiol Renal Physiol* 2001;280:F786–F793.
145. Li D, Wang Z, Sun P, Jin Y, Lin DH, Hebert SC, Giebisch G, Wang WH. Inhibition of MAPK stimulates the Ca^{2+}-dependent big-conductance K channels in cortical collecting duct. *Proc Natl Acad Sci USA* 2006;103:19569–19574.
146. Pacha J, Frindt G, Sackin H, Palmer LG. Apical maxi K channels in intercalated cells of CCT. *Am J Physiol* 1991;261:F696–F705.

147. Liu W, Xu S, Woda C, Kim P, Weinbaum S, Satlin LM. Effect of flow and stretch on the $[Ca^{2+}]i$ response of principal and intercalated cells in cortical collecting duct. *Am J Physiol Renal Physiol* 2003;285: F998–F1012.
148. Palmer LG, Frindt G. High-conductance K channels in intercalated cells of the rat distal nephron. *Am J Physiol Renal Physiol* 2007;292: F966–F973.
149. Taniguchi J, Takeda M, Yoshitomi K, Imai M. Pressure- and parathyroid-hormone-dependent Ca^{2+} transport in rabbit connecting tubule: role of the stretch-activated nonselective cation channel. *J Membr Biol* 1994;140:123–132.
150. Pluznick JL, Wei P, Carmines PK, Sansom SC. Renal fluid and electrolyte handling in BKCa-beta1−/− mice. *Am J Physiol Renal Physiol* 2003;284:F1274–F1279.
151. Bailey MA, Cantone A, Yan Q, MacGregor GG, Leng Q, Amorim JB, Wang T, Hebert SC, Giebisch G, Malnic G. Maxi-K channels contribute to urinary potassium excretion in the ROMK-deficient mouse model of Type II Bartter's syndrome and in adaptation to a high-K diet. *Kidney Int* 2006;70:51–59.
152. Finer G, Shalev H, Birk OS, Galron D, Jeck N, Sinai-Treiman L, Landau D. Transient neonatal hyperkalemia in the antenatal (ROMK defective) Bartter syndrome. *J Pediatr* 2003;142:318–323.
153. Rodriguez-Soriano J. Bartter and related syndromes: the puzzle is almost solved. *Pediatr Nephrol* 1998;12:315–327.
154. Simon DB, Karet FE, Rodriguez-Soriano J, Hamdan JH, DiPietro A, Trachtman H, Sanjad SA, Lifton RP. Genetic heterogeneity of Bartter's syndrome revealed by mutations in the K^+ channel, ROMK. *Nat Genet* 1996;14:152–156.
155. Buffin-Meyer B, Younes-Ibrahim M, Barlet-Bas C, Cheval L, Marsy S, Doucet A. K depletion modifies the properties of Sch-28080-sensitive K-ATPase in rat collecting duct. *Am J Physiol* 1997;272: F124–F131.
156. Codina J, DuBose TD, Jr. Molecular regulation and physiology of the H^+, K^+-ATPases in kidney. *Semin Nephrol* 2006;26:345–351.
157. Zhou X, Nakamura S, Xia SL, Wingo CS. Increased CO_2 stimulates K/Rb reabsorption mediated by H-K-ATPase in CCD of potassium-restricted rabbit. *Am J Physiol Renal Physiol* 2001;281:F366–F373.
158. Ahn KY, Turner PB, Madsen KM, Kone BC. Effects of chronic hypokalemia on renal expression of the "gastric" H^+-K^+-ATPase alpha-subunit gene. *Am J Physiol* 1996;270:F557–F566.
159. Silver RB, Mennitt PA, Satlin LM. Stimulation of apical H-K-ATPase in intercalated cells of cortical collecting duct with chronic metabolic acidosis. *Am J Physiol* 1996;270:F539–F547.
160. Palmer LG, Frindt G. Regulation of apical K channels in rat cortical collecting tubule during changes in dietary K intake. *Am J Physiol* 1999;277:F805–F812.
161. Wang W, Lerea KM, Chan M, Giebisch G. Protein tyrosine kinase regulates the number of renal secretory K channels. *Am J Physiol Renal Physiol* 2000;278:F165–F171.
162. Najjar F, Zhou H, Morimoto T, Bruns JB, Li HS, Liu W, Kleyman TR, Satlin LM. Dietary K^+ regulates apical membrane expression of maxi-K channels in rabbit cortical collecting duct. *Am J Physiol Renal Physiol* 2005;289:F922–F932.
163. Silver RB, Soleimani M. H^+-K^+-ATPases: regulation and role in pathophysiological states. *Am J Physiol* 1999;276:F799–F811.
164. Evan AP, Satlin LM, Gattone VH, 2nd, Connors B, Schwartz GJ. Postnatal maturation of rabbit renal collecting duct. II. Morphological observations. *Am J Physiol* 1991;261:F91–F107.
165. Satlin LM, Evan AP, Gattone VH, 3rd, Schwartz GJ. Postnatal maturation of the rabbit cortical collecting duct. *Pediatr Nephrol* 1988;2:135–145.
166. Minuth WW, Gross P, Gilbert P, Kashgarian M. Expression of the alpha-subunit of Na/K-ATPase in renal collecting duct epithelium during development. *Kidney Int* 1987;31:1104–1112.
167. Constantinescu AR, Lane JC, Mak J, Zavilowitz B, Satlin LM. Na^+-K^+-ATPase-mediated basolateral rubidium uptake in the maturing rabbit cortical collecting duct. *Am J Physiol Renal Physiol* 2000;279: F1161–F1168.
168. Satlin LM, Palmer LG. Apical K^+ conductance in maturing rabbit principal cell. *Am J Physiol* 1997;272:F397–F404.
169. Benchimol C, Zavilowitz B, Satlin LM. Developmental expression of ROMK mRNA in rabbit cortical collecting duct. *Pediatr Res* 2000;47:46–52.
170. Zolotnitskaya A, Satlin LM. Developmental expression of ROMK in rat kidney. *Am J Physiol* 1999;276:F825–F836.
171. Woda CB, Miyawaki N, Ramalakshmi S, Ramkumar M, Rojas R, Zavilowitz B, Kleyman TR, Satlin LM. Ontogeny of flow-stimulated potassium secretion in rabbit cortical collecting duct: functional and molecular aspects. *Am J Physiol Renal Physiol* 2003;285: F629–F639.
172. Good DW, Wright FS. Luminal influences on potassium secretion: sodium concentration and fluid flow rate. *Am J Physiol* 1979;236: F192–F205.
173. Stokes JB. Potassium secretion by cortical collecting tubule: relation to sodium absorption, luminal sodium concentration, and transepithelial voltage. *Am J Physiol* 1981;241:F395–F402.
174. Aperia A, Elinder G. Distal tubular sodium reabsorption in the developing rat kidney. *Am J Physiol* 1981;240:F487–F491.
175. Garty H, Palmer LG. Epithelial sodium channels: function, structure, and regulation. *Physiol Rev* 1997;77:359–396.
176. Satlin LM, Sheng S, Woda CB, Kleyman TR. Epithelial Na^+ channels are regulated by flow. *Am J Physiol Renal Physiol* 2001;280: F1010–F1018.
177. Kleyman TR, Roberts C, Ling BN. A mechanism for pentamidine-induced hyperkalemia: inhibition of distal nephron sodium transport. *Ann Intern Med* 1995;122:103–106.
178. Schlanger LE, Kleyman TR, Ling BN. K^+-sparing diuretic actions of trimethoprim: inhibition of Na^+ channels in A6 distal nephron cells. *Kidney Int* 1994;45:1070–1076.
179. Muto S. Potassium transport in the mammalian collecting duct. *Physiol Rev* 2001;81:85–116.
180. Stapleton FB, Nelson B, Vats TS, Linshaw MA. Hypokalemia associated with antibiotic treatment. Evidence in children with malignant neoplasms. *Am J Dis Child* 1976;130:1104–1108.
181. Morimoto T, Liu W, Woda C, Carattino MD, Wei Y, Hughey RP, Apodaca G, Satlin LM, Kleyman TR. Mechanism underlying flow stimulation of sodium absorption in the mammalian collecting duct. *Am J Physiol Renal Physiol* 2006;291:F663–F669.
182. Malnic G, Berliner RW, Giebisch G. Flow dependence of K^+ secretion in cortical distal tubules of the rat. *Am J Physiol* 1989;256: F932–F941.
183. Frindt G, Zhou H, Sackin H, Palmer LG. Dissociation of K channel density and ROMK mRNA in rat cortical collecting tubule during K adaptation. *Am J Physiol* 1998;274:F525–F531.
184. Brandis M, Keyes J, Windhager EE. Potassium-induced inhibition of proximal tubular fluid reabsorption in rats. *Am J Physiol* 1972;222:421–427.
185. Sufit CR, Jamison RL. Effect of acute potassium load on reabsorption in Henle's loop in the rat. *Am J Physiol* 1983;245:F569–F576.
186. Youn JH, McDonough AA. Recent advances in understanding integrative control of potassium homeostasis. *Annu Rev Physiol* 2008. Aug 29[Epub ahead of print].

187. Morita H, Fujiki N, Miyahara T, Lee K, Tanaka K. Hepatoportal bumetanide-sensitive K^+-sensor mechanism controls urinary K^+ excretion. *Am J Physiol Regul Integr Comp Physiol* 2000;278: R1134–R1139.
188. Ahloulay M, Dechaux M, Laborde K, Bankir L. Influence of glucagon on GFR and on urea and electrolyte excretion: direct and indirect effects. *Am J Physiol* 1995;269:F225–F235.
189. Pullman TN, Lavender AR, Aho I. Direct effects of glucagon on renal hemodynamics and excretion of inorganic ions. *Metabolism* 1967;16:358–373.
190. Blachley JD, Crider BP, Johnson JH. Extrarenal potassium adaptation: role of skeletal muscle. *Am J Physiol* 1986;251:F313–F318.
191. Hayslett JP, Binder HJ. Mechanism of potassium adaptation. *Am J Physiol* 1982;243:F103–112.
192. Alexander EA, Levinsky NG. An extrarenal mechanism of potassium adaptation. *J Clin Invest* 1968;47:740–748.
193. Young DB, Smith MJ, Jr., Jackson TE, Scott RE. Multiplicative interaction between angiotensin II and K concentration in stimulation of aldosterone. *Am J Physiol* 1984;247:E328–E335.
194. Engbretson BG, Stoner LC. Flow-dependent potassium secretion by rabbit cortical collecting tubule in vitro. *Am J Physiol* 1987;253: F896–F903.
195. Schwartz GJ, Burg MB. Mineralocorticoid effects on cation transport by cortical collecting tubules in vitro. *Am J Physiol* 1978;235: F576–585.
196. Ikeda U, Hyman R, Smith TW, Medford RM. Aldosterone-mediated regulation of Na^+, K^+-ATPase gene expression in adult and neonatal rat cardiocytes. *J Biol Chem* 1991; 266:12058–12066.
197. Masilamani S, Kim GH, Mitchell C, Wade JB, Knepper MA. Aldosterone-mediated regulation of ENaC alpha, beta, gamma subunit proteins in rat kidney. *J Clin Invest* 1999;104:R19–R23.
198. O'Neil RG, Hayhurst RA. Sodium-dependent modulation of the renal Na-K-ATPase: influence of mineralocorticoids on the cortical collecting duct. *J Membr Biol* 1985;85:169–179.
199. Pacha J, Frindt G, Antonian L, Silver RB, Palmer LG. Regulation of Na channels of the rat cortical collecting tubule by aldosterone. *J Gen Physiol* 1993;102:25–42.
200. Palmer LG, Antonian L, Frindt G. Regulation of apical K and Na channels and Na/K pumps in rat cortical collecting tubule by dietary K. *J Gen Physiol* 1994;104:693–710.
201. Summa V, Mordasini D, Roger F, Bens M, Martin PY, Vandewalle A, Verrey F, Feraille E. Short term effect of aldosterone on Na,K-ATPase cell surface expression in kidney collecting duct cells. *J Biol Chem* 2001;276:47087–47093.
202. Garg LC, Knepper MA, Burg MB. Mineralocorticoid effects on Na-K-ATPase in individual nephron segments. *Am J Physiol* 1981;240: F536–F544.
203. Chen SY, Bhargava A, Mastroberardino L, Meijer OC, Wang J, Buse P, Firestone GL, Verrey F, Pearce D. Epithelial sodium channel regulated by aldosterone-induced protein sgk. *Proc Natl Acad Sci USA* 1999;96:2514–2519.
204. Debonneville C, Flores SY, Kamynina E, Plant PJ, Tauxe C, Thomas MA, Munster C, Chraibi A, Pratt JH, Horisberger JD, Pearce D, Loffing J, Staub O. Phosphorylation of Nedd4-2 by Sgk1 regulates epithelial Na^+ channel cell surface expression. *Embo J* 2001;20: 7052–7059.
205. Wulff P, Vallon V, Huang DY, Volkl H, Yu F, Richter K, Jansen M, Schlunz M, Klingel K, Loffing J, Kauselmann G, Bosl MR, Lang F, Kuhl D. Impaired renal Na^+ retention in the sgk1-knockout mouse. *J Clin Invest* 2002;110:1263–1268.
206. Vallon V, Wulff P, Huang DY, Loffing J, Volkl H, Kuhl D, Lang F. Role of Sgk1 in salt and potassium homeostasis. *Am J Physiol Regul Integr Comp Physiol* 2005;288:R4–R10.
207. Huang DY, Wulff P, Volkl H, Loffing J, Richter K, Kuhl D, Lang F, Vallon V. Impaired regulation of renal K^+ elimination in the sgk1-knockout mouse. *J Am Soc Nephrol* 2004;15:885–891.
208. Attali B, Latter H, Rachamim N, Garty H. A corticosteroid-induced gene expressing an "IsK-like" K^+ channel activity in Xenopus oocytes. *Proc Natl Acad Sci USA* 1995;92:6092–6096.
209. Capurro C, Coutry N, Bonvalet JP, Escoubet B, Garty H, Farman N. Cellular localization and regulation of CHIF in kidney and colon. *Am J Physiol* 1996;271:C753–C762.
210. Garty H, Lindzen M, Scanzano R, Aizman R, Fuzesi M, Goldshleger R, Farman N, Blostein R, Karlish SJ. A functional interaction between CHIF and Na-K-ATPase: implication for regulation by FXYD proteins. *Am J Physiol Renal Physiol* 2002;283:F607–F615.
211. Wald H, Goldstein O, Asher C, Yagil Y, Garty H. Aldosterone induction and epithelial distribution of CHIF. *Am J Physiol* 1996;271:F322–F329.
212. Van Acker KJ, Scharpe SL, Deprettere AJ, Neels HM. Renin-angiotensin-aldosterone system in the healthy infant and child. *Kidney Int* 1979;16:196–203.
213. Aperia A, Broberger O, Herin P, Zetterstrom R. Sodium excretion in relation to sodium intake and aldosterone excretion in newborn pre-term and full-term infants. *Acta Paediatr Scand* 1979;68: 813–817.
214. Robillard JE, Nakamura KT, Lawton WJ. Effects of aldosterone on urinary kallikrein and sodium excretion during fetal life. *Pediatr Res* 1985;19:1048–1052.
215. Stephenson G, Hammet M, Hadaway G, Funder JW. Ontogeny of renal mineralocorticoid receptors and urinary electrolyte responses in the rat. *Am J Physiol* 1984;247:F665–F671.
216. Field MJ, Giebisch GJ. Hormonal control of renal potassium excretion. *Kidney Int* 1985;27:379–387.
217. West ML, Bendz O, Chen CB, Singer GG, Richardson RM, Sonnenberg H, Halperin ML. Development of a test to evaluate the transtubular potassium concentration gradient in the cortical collecting duct in vivo. *Miner Electrolyte Metab* 1986;12:226–233.
218. West ML, Marsden PA, Richardson RM, Zettle RM, Halperin ML. New clinical approach to evaluate disorders of potassium excretion. *Miner Electrolyte Metab* 1986;12:234–238.
219. Rodriguez-Soriano J, Ubetagoyena M, Vallo A. Transtubular potassium concentration gradient: a useful test to estimate renal aldosterone bio-activity in infants and children. *Pediatr Nephrol* 1990;4: 105–110.
220. Malnic G, De Mello Aires M, Giebisch G. Potassium transport across renal distal tubules during acid-base disturbances. *Am J Physiol* 1971;221:1192–1208.
221. Boudry JF, Stoner LC, Burg MB. Effect of acid lumen pH on potassium transport in renal cortical collecting tubules. *Am J Physiol* 1976;230:239–244.
222. Tabei K, Muto S, Furuya H, Sakairi Y, Ando Y, Asano Y. Potassium secretion is inhibited by metabolic acidosis in rabbit cortical collecting ducts in vitro. *Am J Physiol* 1995;268:F490–F495.
223. Wang WH, Schwab A, Giebisch G. Regulation of small-conductance K^+ channel in apical membrane of rat cortical collecting tubule. *Am J Physiol* 1990;259:F494–F502.
224. Beck FX, Dorge A, Rick R, Schramm M, Thurau K. The distribution of potassium, sodium and chloride across the apical membrane of renal tubular cells: effect of acute metabolic alkalosis. *Pflugers Arch* 1988;411:259–267.

225. Stone DK, Seldin DW, Kokko JP, Jacobson HR. Mineralocorticoid modulation of rabbit medullary collecting duct acidification. A sodium-independent effect. *J Clin Invest* 1983;72:77–83.
226. Kone BC, Higham SC. A novel N-terminal splice variant of the rat H^+-K^+-ATPase alpha2 subunit. Cloning, functional expression, and renal adaptive response to chronic hypokalemia. *J Biol Chem* 1998;273:2543–2552.
227. Aizman RI, Celsi G, Grahnquist L, Wang ZM, Finkel Y, Aperia A. Ontogeny of K^+ transport in rat distal colon. *Am J Physiol* 1996;271: G268–G274.
228. Foster ES, Hayslett JP, Binder HJ. Mechanism of active potassium absorption and secretion in the rat colon. *Am J Physiol* 1984;246: G611–G617.
229. Butterfield I, Warhurst G, Jones MN, Sandle GI. Characterization of apical potassium channels induced in rat distal colon during potassium adaptation. *J Physiol* 1997;501(Pt 3):537–547.
230. Dawson DC. Ion channels and colonic salt transport. *Annu Rev Physiol* 1991;53:321–339.
231. Pacha J, Popp M, Capek K. Corticosteroid regulation of Na^+ and K^+ transport in the rat distal colon during postnatal development. *J Dev Physiol* 1988;10:531–540.
232. Sausbier M, Matos JE, Sausbier U, Beranek G, Arntz C, Neuhuber W, Ruth P, Leipziger J. Distal colonic K^+ secretion occurs via BK channels. *J Am Soc Nephrol* 2006;17:1275–1282.
233. Warth R, Bleich M. K^+ channels and colonic function. *Rev Physiol Biochem Pharmacol* 2000;140:1–62.
234. Kunzelmann K, Mall M. Electrolyte transport in the mammalian colon: mechanisms and implications for disease. *Physiol Rev* 2002;82:245–289.
235. Binder HJ, McGlone F, Sandle GI. Effects of corticosteroid hormones on the electrophysiology of rat distal colon: implications for Na^+ and K^+ transport. *J Physiol* 1989;410:425–441.
236. Rechkemmer G, Frizzell RA, Halm DR. Active potassium transport across guinea-pig distal colon: action of secretagogues. *J Physiol* 1996;493(Pt 2):485–502.
237. Agarwal R, Afzalpurkar R, Fordtran JS. Pathophysiology of potassium absorption and secretion by the human intestine. *Gastroenterology* 1994;107:548–571.
238. Hayes CP, Jr., McLeod ME, Robinson RR. An extrarenal mechanism for the maintenance of potassium balance in severe chronic renal failure. *Trans Assoc Am Physicians* 1967;80:207–216.
239. Sandle GI, Gaiger E, Tapster S, Goodship TH. Enhanced rectal potassium secretion in chronic renal insufficiency: evidence for large intestinal potassium adaptation in man. *Clin Sci (Lond)* 1986;71:393–401.
240. Sandle GI, Gaiger E, Tapster S, Goodship TH. Evidence for large intestinal control of potassium homoeostasis in uraemic patients undergoing long-term dialysis. *Clin Sci (Lond)* 1987;73: 247–252.
241. Mathialahan T, Maclennan KA, Sandle LN, Verbeke C, Sandle GI. Enhanced large intestinal potassium permeability in end-stage renal disease. *J Pathol* 2005;206:46–51.
242. Aizman R, Aizman O, Celsi G. Beta-adrenergic stimulation of cellular K^+ uptake in rat distal colon. *Acta Physiol Scand* 1998;164: 309–315.