Renal Potassium Handling in Healthy and Sick Newborns

Hao Zhou* and Lisa M. Satlin†

Growing infants must maintain a state of positive K⁺ balance, a task accomplished, in large part, by the kidney. The distal nephron is uniquely adapted to retain total body K⁺ early in life. The magnitude and direction of net K⁺ transport in the cortical collecting duct (CCD), the segment responsible for the final renal regulation of K⁺ balance in the adult, reflect the balance of opposing fluxes of K⁺ secretion and K⁺ absorption. Evidence now indicates that the low capacity of the neonatal CCD for K⁺ secretion is due, at least in part, to a relative paucity of conducting K⁺ channels in the urinary membrane. A relative excess of K⁺ absorption in this nephron segment may further reduce net urinary K⁺ secretion. Under conditions prevailing in vivo, the balance of fluxes in the CCD likely contributes to the relative K⁺ retention characteristic of the neonatal kidney.

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Potassium (K⁺) is the most abundant intracellular cation (100-150 mEq/liter) and plays an important role in a variety of cell functions, including cell growth and division, DNA and protein synthesis, conservation of cell volume and pH, and optimal enzyme function. Approximately 98% of the total body K⁺ content in the adult resides within cells, primarily muscle, whereas the remaining 2% is located in the extracellular fluid (Fig 1). The extracellular K⁺ concentration (generally ranging from 3.5-5.0 mEq/liter) is tightly regulated by mechanisms that govern the distribution between the intra- and extra-cellular compartments and balance between intake and output. The steep K⁺ (and sodium) concentration gradients across cell membranes are maintained by the ubiquitous Na-K-adenosine triphosphatase (Na-K-ATPase), an enzyme present on the surface of essentially all eukaryotic cells (Fig 2).

K⁺ Homeostasis

The homeostatic goal of the adult is to remain in zero K⁺ balance. Thus, approximately 90% to 95% of the typical daily K⁺ intake of 1 mEq per kilogram body weight is ultimately eliminated from the body in the urine; the residual 5% to 10% of the daily K⁺ load is lost through the stool. Normally, the amount of K⁺ lost through the sweat is negligible (Fig 1).

In contrast to the adult, infants greater than approximately 30 weeks gestational age (GA) must maintain a state of positive K⁺ balance.¹ The net accretion of K⁺ is necessary to ensure the availability of adequate substrate for incorporation into cells newly formed during periods of somatic growth. Postnatal growth is associated with an increase in total body K⁺ from approximately 8 mEq/cm body height at birth to >14 mEq/cm body height by 18 years of age.³ The rate of accretion of body K⁺ per kilogram body weight in the infant is more rapid than in the older child and adolescent, likely reflecting both an increase in cell number and K⁺ concentration, at least in skeletal muscle, with advancing age (Fig 3).⁴,⁶

The tendency to retain K⁺ early in postnatal life is reflected in the observation that infants, particularly premature newborns, tend to have higher plasma K⁺ values than children.²,⁷,⁸,¹¹ Of note is that in fetal life, K⁺ is actively transported across the placenta from mother to fetus.¹² Indeed, the fetal K⁺ concentration is maintained at levels exceeding 5 mEq/liter even in the face of maternal K⁺ deficiency.¹²,¹³

Nonoliguric hyperkalemia, defined as a serum K⁺ concentration of >6.5 mEq/liter, is ob-
served in 30% to 50% of very low birth weight (VLBW) infants, in the absence of K⁺ intake, during the first 48 hours of life, but not in mature infants or VLBW infants after 72 hours of age. This biochemical observation reflects a shift of K⁺ from the intra- to the extra-cellular fluid space, possibly related to Na-K pump failure, as well as a limited renal K⁺ secretory capacity, as discussed below. Prenatal steroid treatment may prevent nonoliguric hyperkalemia by upregulating Na-K-ATPase pump activity in the fetus, thereby stabilizing the cell membrane to prevent a shift of K⁺ out of cells.

**K⁺ Intake and Output**

In the adult, urinary K⁺ excretion varies considerably, depending in large part on dietary intake. Typically, adults that consume an average American diet that contains more sodium (Na⁺) than K⁺ excrete urine with a Na⁺-to-K⁺ ratio greater than one. Although breast milk and commercially available infant formulas generally provide Na⁺ to K⁺ in a ratio of approximately 0.5 to 0.6, the urinary Na⁺ to K⁺ ratio in the newborn typically exceeds one. Whereas a high urinary Na⁺ to K⁺ ratio in the premature infant may reflect the salt wasting characteristic of newborns <34 weeks GA, this finding in the full-term newborn may be explained by a greater requirement for K⁺ over Na⁺ during growth and/or a relative hyporesponsiveness of the neonatal kidney to mineralocorticoid activity.
Regulation of K+/H11001 Balance by Redistribution

The daily dietary intake of K+/H11001 in the adult generally approaches or exceeds the total K+/H11001 normally present within the extracellular fluid space (Fig 1). Although K+ balance in the adult ultimately depends on the timely renal elimination of dietary intake, the renal excretion of K+/H11001 is relatively sluggish, requiring from 6 to 12 hours to be accomplished. Life-threatening hyperkalemia is not generally observed during this interval due to the rapid (within minutes) hormonally-mediated translocation of extracellular K+/H11001 into cells, a response mediated by the Na-K-ATPase (Fig 2). The hormonal, as well as other chemical and physical factors that acutely influence K+ redistribution, are listed in Table 1.

Regulation Of K+ Balance Through Renal Excretion

The processes involved in renal K+ handling include filtration, reabsorption, and secretion (Fig 4). Filtered K+ is reabsorbed almost entirely in proximal segments of the nephron; urinary K+ excretion, at least in the adult, is accomplished by K+ secretion in the distal segments of the nephron.

It is now well established that the neonatal kidney contributes to K+ retention early in life. In newborns, the renal K+ clearance is low, even when corrected for their low glomerular filtration rate. In response to exogenous K+ loading, infants like adults, can excrete K+ at a rate that exceeds its filtration, indicating the capacity for net tubular secretion. However, the rate of K+ excretion expressed either per unit body weight or kidney weight in infants and young animals subject to exogenous K+ loading is less than that observed in older animals.

In a longitudinal prospective study of 23- to 31-week GA infants, the fractional excretion of K+ fell by half between 26 and 30 weeks GA, a developmental change that was not accompanied by a significant change in absolute urinary...

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**Table 1. Factors, Relevant to the Infant, that Acutely Regulate the Redistribution of K+ Between the Intra- and Extra-Cellular Space**

<table>
<thead>
<tr>
<th>Effect on cell uptake of K+</th>
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<tbody>
<tr>
<td><strong>Physiologic</strong></td>
</tr>
<tr>
<td>plasma K concentration ↓</td>
</tr>
<tr>
<td>insulin ↑</td>
</tr>
<tr>
<td>catecholamines ↓</td>
</tr>
<tr>
<td>a-agonists ↑</td>
</tr>
<tr>
<td>b-agonists ↓</td>
</tr>
<tr>
<td><strong>Pathologic</strong></td>
</tr>
<tr>
<td>acid-base balance ↓</td>
</tr>
<tr>
<td>acidosis ↑</td>
</tr>
<tr>
<td>alkalosis ↓</td>
</tr>
<tr>
<td>hyperosmolality ↑ cell efflux</td>
</tr>
<tr>
<td>cell breakdown ↓ cell efflux</td>
</tr>
</tbody>
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![Figure 3. Relationship between total body K+ (g) and height (cm) for infants and children. The rate of accretion of body K+ in the neonate is more rapid than in later childhood, likely reflecting both an increase in cell number and K+ concentration, at least in skeletal muscle, with advancing age.](image1)

![Figure 4. Sites of K+ transport along successive tubular segments of the fully differentiated nephron. Arrows identify the direction of net K+ transport as either out of (reabsorption) or into (secretion) the urinary fluid. See text for details. (Reprinted with permission.56).](image2)
K⁺ excretion.\(^1\) Given that the filtered load of K⁺ increased almost 3-fold during this same time interval, the constancy of renal K⁺ excretion could best be explained by a developmental increase in the capacity of the kidney for K⁺ reabsorption.\(^1\)

In general, the limited K⁺ excretory capacity of the immature kidney becomes clinically relevant only under conditions of K⁺ excess. As stated earlier, under normal circumstances, K⁺ retention by the newborn kidney is appropriate and is required for multiple cellular processes including somatic growth.

**Sites of K⁺ Transport Along the Nephron**

K⁺ is freely filtered at the glomerulus (Fig 4). Studies in both suckling and adult animals indicate that approximately 65% of the filtered load of K⁺ is reabsorbed along the proximal tubule (Fig 4).\(^{19,21,22}\) Reabsorption is passive in this segment, closely following water reabsorption. Only ~10% of the filtered load of K⁺ reaches the early distal tubule of the adult, indicating that a significant amount of K⁺ has been reabsorbed in the intervening segments, specifically across the thick ascending limb of the loop of Henle (TALH; Fig 4).\(^{19}\) In contrast, up to 35% of the filtered load of K⁺ reaches the distal tubule of the newborn rat.\(^{21}\) This suggests that postnatal maturation of the TALH is characterized by a developmental increase in its capacity for K⁺ reabsorption. The additional observations that both the diluting capacity and TALH Na-K-ATPase activity also increase after birth are consistent with this notion.\(^{23,24}\)

K⁺ reabsorption in the TALH is mediated by a Na-K-2Cl cotransporter that translocates one K⁺ ion into the cell accompanied by one Na⁺ and two chloride ions (Fig 5A). Transporter activity is ultimately driven by the basolateral Na-K-ATPase, which generates and maintains a low intracellular Na⁺ concentration and thus a chemical gradient favoring Na⁺ entry at the apical membrane. Activity of the Na-K-2Cl transporter requires the presence of a K⁺ conductance in the apical (urinary) membrane to recycle K⁺ across this membrane, thus ensuring an abundant supply of substrate for the cotransporter. Diuretics such as furosemide and bumetanide that inhibit the Na-K-2Cl cotransporter block K⁺ (as well as Na⁺) reabsorption at this site and uncover K⁺ secretion, leading to profound urinary K⁺ losses.

The K⁺ channel present in the urinary membrane of the TALH (and cortical collecting duct; see below) is believed to be encoded by the ROMK gene.\(^{19,25,26}\) Loss-of-function mutations in ROMK lead to antenatal Bartter syndrome, also known as the hyperprostaglandin E syndrome, which is characterized by severe renal salt and fluid wasting, consistent with a pattern of impaired TALH function.\(^{27}\) The typical presentation includes polyhydramnios, premature delivery, and life-threatening episodes of dehydration during the first week of life. This group of patients also has severe growth failure, hypercalciuria, and early-onset nephrocalcinosis.

![Figure 5](Zhou and Satlin 106)

**Figure 5.** K⁺ (and Na⁺) transport pathways in the fully differentiated nephron. The major transport proteins involved in K⁺ and Na⁺ transport are shown for the (A) thick ascending limb of Henle (TALH) and cortical collecting duct, a nephron segment comprised of (B) principal and (C) intercalated cells. See text for details regarding the transport pathways shown. (Reprinted with permission.\(^{56}\)).
Under baseline conditions in the adult, regulated $K^+$ secretion by the distal tubule and the cortical collecting duct (CCD) (Fig 4) contributes prominently to urinary $K^+$ excretion, which can approach 20% of the filtered load. In contrast to the high rate of $K^+$ secretion observed in CCDs isolated from adult rabbits and studied when perfused at physiological flow rates in vitro, segments isolated from neonatal animals show no significant net $K^+$ transport until after the third week of postnatal life. By 6 weeks of age, the rate of net $K^+$ secretion in the CCD is comparable to that observed in the adult. These results indicate that the low rates of $K^+$ excretion characteristic of the newborn kidney are due, at least in part, to a low $K^+$ secretory capacity of the CCD.

The CCD is comprised of 2 cell populations. Principal cells (Fig 5B) reabsorb $Na^+$ and secrete $K^+$, whereas intercalated cells (Fig 5C) primarily function in acid-base homeostasis but can reabsorb $K^+$ in response to dietary $K^+$ restriction or metabolic acidosis. Thus, the direction and magnitude of net $K^+$ transport in this segment represents the balance of $K^+$ secretion and absorption, opposing processes mediated by principal and intercalated cells, respectively.

$K^+$ secretion. $K^+$ secretion in the CCD is accomplished by a two-step process. First, $K^+$ is actively taken up into the principal cell at the basolateral membrane in exchange for $Na^+$, a process mediated by the Na-K-ATPase (Fig. 5B). The high intracellular $K^+$ concentration and lumen-negative voltage within the CCD, generated by apical $Na^+$ entry across epithelial $Na^+$ channels (ENaCs) and its electrogenic basolateral extrusion, create an electrochemical gradient that favors the passive diffusion of cell $K^+$ into the luminal fluid through apical $K^+$-selective channels. The small conductance secretory $K^+$ (SK) channel, encoded by the ROMK gene, is considered to mediate baseline $K^+$ secretion in this nephron segment. In sum, $K^+$ secretion in the CCD requires $Na^+$ absorption (to establish the electrochemical gradient) and the presence of $K^+$-selective channels in the urinary membrane. Any factor that enhances the electrochemical driving force or increases the apical membrane permeability to $K^+$ will favor $K^+$ secretion.

The limited capacity of the neonatal CCD for baseline net $K^+$ secretion appears not to be due to an unfavorable electrochemical gradient. Although Na-K-ATPase activity in the neonatal collecting duct is only ~50% of that measured in the mature nephron, intracellular $K^+$ concentration in this secretory epithelium at birth is comparable to that measured in the adult (presumably reflecting a relative paucity of membrane $K^+$ channels early in life). The rate of net $Na^+$ absorption in the CCD at 2 weeks of age is ~60% of that measured in the adult and is not considered to be limiting for $K^+$ secretion. Cumulative evidence now suggests that the postnatal increase in CCD $K^+$ secretory capacity is due to a developmental increase in number of $SK$ channels, reflecting an increase in transcription and translation of functional ROMK channel proteins. Molecular analyses demonstrate that ROMK mRNA and protein are first detectable in the second week of postnatal life in the rodent, immediately preceding the appearance of functional channels and $K^+$ secretion in this segment.

$K^+$ absorption. The distal nephron of $K^+$-depleted adults may reabsorb $K^+$. This process is mediated by a hydrogen, potassium adenosine triphosphatase (H-K-ATPase), an enzyme, present at the apical membrane of acid-base transporting intercalated cells, that exchanges a single $K^+$ for a proton (Fig 5C). Fluorescent functional assays identify significant activity of the apical H-K-ATPase in neonatal intercalated cells, suggesting that the collecting duct is poised to retain urinary $K^+$ early in life. As stated earlier, clearance studies in premature infants of <30 weeks GA suggest a developmental increase in the capacity of the kidney for $K^+$ reabsorption. Similar studies in saline-expanded dogs provide indirect evidence for a diminished secretory and enhanced reabsorptive capacity of the immature distal nephron to $K^+$.

Luminal and Peritubular Factors that Regulate Net $K^+$ Transport in the CCD

$Na^+$ delivery and absorption. As predicted from the principal cell model (Fig 5B), the magnitude of $Na^+$ absorption determines the electrochemical driving force for $K^+$ diffusion into the lumen. The dependence of $K^+$ secretion on distal $Na^+$ delivery becomes evident at tubular fluid $Na^+$ concentrations of less than 30 mEq/liter, a
value below which K⁺ secretion falls sharply.³⁵,³⁶ In vivo measurements of the Na⁺ concentration in distal tubular fluid generally exceed 35 mmol/L both in adult and suckling rats and thus would not be expected to restrict distal K⁺ secretion.³⁷

Extracellular volume expansion or administration of many diuretics (osmotic diuretics, carbonic anhydrase inhibitors, loop and thiazide diuretics) is accompanied by an increase in urinary excretion of both Na⁺ and K⁺. The kaliuresis is mediated not only by the increased delivery of Na⁺ to the distal nephron, but also by the increased tubular fluid flow rate, which maximizes the chemical driving forces, as described below, favoring K⁺ secretion. Other K⁺-sparing diuretics, such as amiloride and triamterene, block distal Na⁺ reabsorption, which reduces the electrical potential gradient favoring K⁺ secretion.

Na⁺ delivered to the distal nephron is generally accompanied by chloride. Chloride reabsorption, which occurs predominantly via the paracellular pathway, tends to reduce the lumen-negative potential that would otherwise drive K⁺ secretion. When Na⁺ is accompanied by an anion less reabsorbable than chloride, such as bicarbonate (as in proximal renal tubular acidosis), β-hydroxybutyrate (in diabetic ketoacidosis) or carbenicillin (during antibiotic therapy), luminal electronegativity is maintained, thereby eliciting more K⁺ secretion than occurs with a comparable Na⁺ load delivered with chloride.

**Tubular fluid (urinary) flow rate.** K⁺ secretion in the mature CCD is strongly stimulated by an increase in urinary flow rate, as follows volume expansion or administration of diuretics. However, the developmental appearance of flow-stimulated K⁺ secretion, studied in single rabbit CCDs, does not appear until the 5th week of postnatal life, ~2 weeks after baseline K⁺ secretion is first detected (Fig 6).²⁸,³⁸ Recent evidence suggests that flow-dependent K⁺ secretion is mediated by a stretch- and calcium-activated high-conductance maxi-K channel.³⁸,³⁹ Maxi-K channel mRNA and protein are not consistently detected in the CCD until the 4th week of life,³⁸ suggesting that the postnatal appearance of flow-dependent K⁺ secretion is determined by the transcriptional and/or translational regulation of expression of maxi-K channels in the distal nephron. It should also be noted that the higher the urinary flow rate in the distal nephron, the slower the rate of rise of tubular fluid K⁺ concentration as secreted K⁺ is rapidly diluted in urine of low K⁺ concentration. Maintenance of a relatively low tubular fluid K⁺ concentration maximizes the K⁺ concentration gradient and thus chemical driving force favoring net K⁺ secretion.

**K⁺ intake.** The adult kidney responds to an increase in K⁺ intake with an increase in urinary K⁺ excretion within ~1 to 2 days.⁴⁰ The adaptation to a high-K⁺ diet is associated with an increase in density of conducting apical SK channels in the CCD within 6 hours.⁴¹ Apical Na⁺ channel and basolateral Na-K pump activity also increase under these same conditions, changes expected to enhance the electrochemical gradient favoring K⁺ secretion.⁴² The increases in SK channel activity and K⁺ secretion are not medi-
ated by an increase in circulating levels of mineralocorticoids alone, but depend upon a high plasma K⁺ concentration.⁴⁰ High plasma K⁺ levels have been suggested to lead to release an as yet unidentified kaliuretic hormone from the central nervous system through a reflex involving receptors in the gut or portal vein.⁵³

When K⁺ intake is chronically reduced, K⁺ secretion by principal cells falls, in the absence of any change in density of apical SK channels in the CCD,⁴⁰ whereas K⁺ reabsorption by intercalated cells is stimulated.⁴⁴ Stimulation of H-K-ATPase activity in intercalated cells results not only in K⁺ retention, but also urinary acidification and metabolic alkalosis.

**Acid-base balance.** Disorders of acid-base homeostasis can alter tubular K⁺ secretion. Acute metabolic acidosis reduces cell K⁺ concentration and leads to a reduction in urine pH, which in turn inhibits apical SK/ROMK channel activity.⁴⁵,⁴⁶ The net effect is a fall in urinary K⁺ excretion.⁴⁷ Chronic metabolic acidosis has variable effects on urinary K⁺ excretion. In chronic metabolic acidosis, K⁺ secretion is influenced by modifications of the glomerular filtrate (eg, chloride and bicarbonate concentration), tubular fluid flow rate, and circulating aldosterone levels.

Both acute respiratory alkalosis and metabolic alkalosis result in increases in urine pH and K⁺ excretion. The alkalosis-induced stimulation of K⁺ secretion reflects 2 direct effects on principal cells: 1) stimulation of basolateral K⁺ uptake and 2) an increase in the permeability of the apical membrane to K⁺ due to an increase in duration of time the SK/ROMK channels remain open.⁴⁹

**Mineralocorticoids.** The role of aldosterone in stimulating K⁺ secretion in the fully differentiated CCD is well established.⁴⁸,⁴⁹ In the adult, the mineralocorticoid-induced stimulation of renal K⁺ secretion is considered to be due primarily to an increase in the electrochemical driving force favoring K⁺ exit across the apical membrane, generated by stimulation of apical Na⁺ entry and reabsorption.

Aldosterone action requires its initial binding to the mineralocorticoid receptor, followed by translocation of the hormone-receptor complex to the nucleus where specific genes are stimulated to code for physiologically active proteins. Cellular effects within the fully differentiated CCD include increases in the density of active ENaC Na⁺ channels, due to recruitment of intracellular channels to the apical membrane, de novo synthesis of ENaC subunits and activation of pre-existing channels.⁵⁰,⁵¹ Aldosterone also stimulates Na,K-ATPase activity through both recruitment of intracellular pumps and increased total amounts of Na pump subunits.⁵² The net effect of these actions is the stimulation of net Na⁺ absorption, leading to an increase in lumen negative transepithelial voltage, thereby facilitating net K⁺ secretion. The effects of aldosterone on ENaC and, to some extent, the Na-K pump appear to be indirect, mediated by aldosterone-induced proteins.⁵³

Plasma aldosterone concentrations in the premature infant and newborn are high compared to those in the adult.²,⁵⁴ The density of aldosterone binding sites, receptor affinity, and degree of nuclear binding of hormone-receptor appear to be similar in mature and immature rats.¹⁸ Yet, clearance studies in fetal and newborn animals demonstrate a relative insensitivity of the immature kidney to the hormone, presumably due to a postreceptor phenomenon.²,¹⁸,⁵⁵ Measurements of the transtubular potassium gradient (urine K⁺ concentration divided by the urine-to-plasma osmolality ratio), an index of the K⁺ secretory capacity of the distal nephron, have been reported to be lower in 27 than 30-week GA preterm infants followed over the first 5 weeks of postnatal life.⁹ The low transtubular potassium gradient has been attributed to a state of relative hypoaldosteronism,⁹ but may also reflect the absence of K⁺ secretory transport pathways (ie, channel proteins).

## Summary

Infants greater than approximately 30 weeks GA and young children must maintain a state of

<table>
<thead>
<tr>
<th>Luminal:</th>
<th>Na⁺ delivery and absorption</th>
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<tr>
<td>Tubular fluid flow rate</td>
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<table>
<thead>
<tr>
<th>Peritubular:</th>
<th>K⁺ intake</th>
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<tr>
<td>alkalosis</td>
<td></td>
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<td>hormones (mineralocorticoids)</td>
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positive K⁺ balance for somatic growth. The kidney is the primarily organ responsible for regulation of external K⁺ balance. Kidneys of full-term newborn humans and animals conserve K⁺. The CCD within the distal nephron is uniquely adapted to retain total body K⁺ early in life. In contrast to the brisk net K⁺ secretion detected in single CCDs isolated from adult animals, CCDs isolated from newborns show no net K⁺ secretion during the few weeks of postnatal life. The magnitude and direction of net K⁺ transport in the CCD reflect the balance of opposing fluxes of K⁺ secretion and K⁺ absorption, mediated by principal and intercalated cells, respectively. Evidence now indicates that the low capacity of the CCD for K⁺ secretion early in life is due to a limited capacity of principal cells for K⁺ secretion, reflecting, at least in part, a relative paucity of conducting K⁺ (SK/ROMK and maxi-K) channels in the urinary membrane. A relative excess of K⁺ absorption by adjacent intercalated cells in this nephron segment may further reduce net urinary K⁺ secretion. Under conditions prevailing in vivo, the balance of fluxes mediated by these 2 cell types likely contributes to the relative K⁺ retention characteristic of the neonatal kidney.

References

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