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EDUCATIONAL REVIEW

# Developmental changes in renal tubular transport—an overview

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**Abstract** The adult kidney maintains a constant volume and composition of extracellular fluid despite changes in water and salt intake. The neonate is born with a kidney that has a small fraction of the glomerular filtration rate of the adult and immature tubules that function at a lower capacity than that of the mature animal. Nonetheless, the neonate is also able to maintain a constant extracellular fluid volume and composition. Postnatal renal tubular development was once thought to be due to an increase in the transporter abundance to meet the developmental increase in glomerular filtration rate. However, postnatal renal development of each nephron segment is quite complex. There are isoform changes of several transporters as well as developmental changes in signal transduction that affect the capacity of renal tubules to reabsorb solutes and water. This review will discuss neonatal tubular function with an emphasis on the differences that have been found between the neonate and adult. We will also discuss some of the factors that are responsible for the maturational changes in tubular transport that occur during postnatal renal development.

**Keywords** Renal development · Sodium transport · Nephron · Ontogeny of renal transport

This review focuses on the postnatal developmental changes that occur in tubular transport. While not the objective of this review, it is important to understand that there are changes in the glomerular filtration rate and thus delivery of solutes and water during renal development. The glomerular filtration rate of a term newborn is only 2 ml/min compared to 100–120 ml/min in the adult [1]. If one normalizes the glomerular filtration rate to an adult's body surface area, the glomerular filtration rate increases fourfold during the first 1–2 years of life, at which point the adult glomerular filtration rate is attained [2, 3]. This developmental change in glomerular filtration rate is not due to an increase in glomerular number as no new nephrons are formed after 34–36 weeks of gestation. However, there are changes in renal hemodynamics and the glomerular basement membrane that result in an increase in the glomerular filtration rate during postnatal development. The most important factor that leads to an increase in glomerular filtration rate is the postnatal increase in glomerular surface area [4, 5]. If there was no increase in solute and water reabsorption that parallels the increase in glomerular filtration, the neonate would become volume-depleted with a minor developmental increase in glomerular filtration rate [6, 7]. Thus, there is a balance between changes in glomerular filtration rate and transport designated glomerulotubular balance. Glomerulotubular balance persists in the adult nephron so that changes in glomerular filtration rate seen with changes in extracellular fluid volume are paralleled by appropriate changes in tubular transport. However, in very premature neonates, there is some glomerulotubular imbalance evidenced by glucosuria, with normal serum glucose levels [1, 8, 9]. This overview of developmental changes in tubular transport will focus on the major changes that occur in renal transport mechanisms during postnatal development. There are also developmental differences in hormone levels that regulate tubular transport, as well as hormone receptor abundance, signal transduction and tubular response to various hormones that occur during postnatal development that are beyond the scope of the current review.

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## Proximal tubule

The proximal tubule receives the glomerular ultrafiltrate, which is isotonic to plasma. The proximal tubule is

responsible for the bulk reclamation of the glomerular filtrate. The proximal tubule reabsorbs all of the filtered glucose and amino acids, the vast majority of filtered phosphate as well as 80 % of the filtered bicarbonate and two-thirds of the filtered chloride [10]. The proximal tubule is very permeable to water and the luminal fluid remains isotonic to plasma during the entire course along this nephron segment. The early portion of the proximal tubule reabsorbs most of the filtered glucose and amino acids and most of the filtered bicarbonate that will be reabsorbed by this segment. This leaves the late proximal tubule with a higher luminal chloride and lower luminal bicarbonate concentration than the peritubular plasma. In the latter parts of the proximal tubule, NaCl is reabsorbed by active and passive means as will be discussed below. An illustration of a proximal tubular cell is shown in Fig. 1.

The rate of proximal tubule transport is significantly less in the neonate than in the adult segment. In utero and in premature infants born before 34 weeks gestation, nephrons are still being formed. Nephron formation occurs in a centrifugal fashion with juxtamedullary nephrons much more mature than those of the superficial cortex [11]. There is a developmental increase in proximal tubular transport in both superficial and juxtamedullary nephrons, but the increase is more profound in the superficial nephrons [12, 13]. As in the adult, transport by the neonatal proximal tubule is isotonic. As solutes are reabsorbed, water moves through cells through water channels designated aquaporin 1. Aquaporin 1 water channels are present in most cells in the body so that the intracellular and extracellular osmolality are equal. The rate of volume absorption by proximal tubular transport is dependent on the combined rate of transport of the individual solutes absorbed. Most solute transport is secondary to active transport, but there is also a component of passive solute transport that occurs along the paracellular pathway.

Most transport along the nephron is sodium dependent, where the low intracellular sodium generated by the $Na^+/K^+$-ATPase provides the driving force for sodium across the apical membrane. $Na^+/K^+$-ATPase is a heterodimer consisting primarily of $\alpha$ and $\beta$ subunits. The $\alpha$-subunit is the catalytic unit that binds sodium, potassium, and ATP. The $\beta$-subunit is essential for targeting the $\alpha$-subunit to the cell membrane and stabilizing the $Na^+/K^+$-ATPase preventing its movement from the basolateral membrane to the apical membrane. There are four isoforms of the $\alpha$-subunit and three isoforms of the $\beta$-subunit; $\alpha 1$ and $\beta 1$ subunits are the primary isoforms in the adult kidney. A $\gamma$ subunit has also been shown to be a part of $Na^+/K^+$-ATPase, but it is not essential for the enzymatic activity of $Na^+/K^+$-ATPase [14, 15].

The neonatal kidney has a lower rate of $Na^+/K^+$-ATPase activity than that of adults. In rodents, the activity increases approximately 3–4 fold in the postnatal period [16, 17]. As with many solutes, the increase in $Na^+/K^+$-ATPase activity occurs at the time of weaning, when there is a rise in serum glucocorticoid and thyroid hormone levels [18, 19]. In addition to evidence that the increase in glucocorticoids and thyroid hormone are responsible for the increase in renal $Na^+/K^+$-ATPase activity [20–22], an increase in apical sodium transport may also be a factor that induces the maturation of $Na^+/K^+$-ATPase on the basolateral membrane [23–26]. The induction of postnatal transport will be covered in detail later in this manuscript.

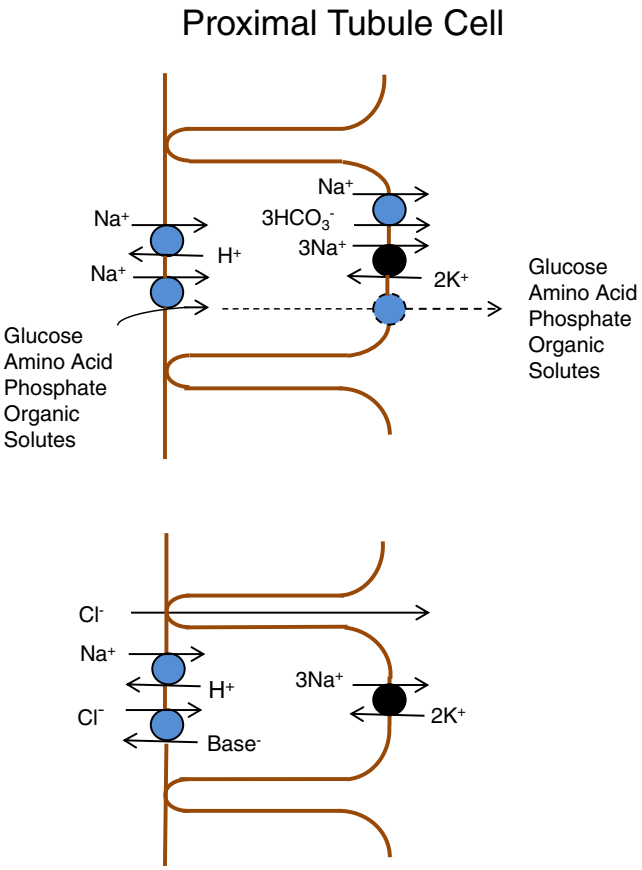


**Fig. 1** Illustration of a proximal tubular cell. The *top cell* is an early proximal tubular cell near the glomerulus depicting the reabsorption of organic solutes and bicarbonate. The lumen is acidified predominantly by an apical $Na^+/H^+$ exchanger. The basolateral $Na^+/K^+$-ATPase lowers intracellular sodium and generates the driving force for this active transport, which is by and large sodium dependent. The *lower cell* depicts a late proximal tubular cell where there is a chloride gradient generated by the preferential reabsorption of bicarbonate over chloride ions in the early proximal tubule. Thus, the late tubular fluid is mostly composed of NaCl, which is actively reabsorbed via the apical $Na^+/H^+$ and $Cl^-$/Base exchangers. The higher luminal chloride provides a concentration gradient for passive chloride transport along the paracellular pathway. Since the concentration of bicarbonate in the blood is greater than the lumen, bicarbonate could diffuse back into the lumen, but the tight junction is quite impermeable to bicarbonate. In this and all figures, the *black circles* depict transporters that require ATP

As an example of organic solute transport, we will discuss glucose transport. Glucose is reabsorbed in an electrogenic fashion with sodium, as shown in Fig. 1. The reabsorption of glucose with sodium leaves the lumen of the proximal tubule with a negative transepithelial potential that is the driving force for the paracellular reabsorption of chloride ions [10]. There are two renal glucose transporters. SGLT1 is a high-

affinity, low-capacity transporter that is expressed in the distal part (S3 segment) of the proximal tubule [27]. SGLT1 transports two sodium ions into the cell for every glucose molecule. This transporter is also present in the intestine and mutations with loss of function of this transporter result in profuse neonatal watery diarrhea due to glucose-galactose malabsorption [28]. SGLT2 is a high-capacity, low-affinity transporter that is present in the early proximal tubule (S1 and S2 segment) where it performs the bulk reclamation of filtered glucose. SGLT2 transports one sodium ion for every glucose molecule. Mutations of this transporter cause familial glucosuria where there is glucosuria without hyperglycemia [29]. There is a developmental increase in glucose transport during development that is due to an increase in the number of transporters as well as an increase in the $Na^+/K^+$-ATPase that provides the driving force for sodium across the apical membrane [13, 30]. The developmental increase in glucose transport is due to an increase in both SGLT1 and SGLT2 [31].

The $Na^+/H^+$ exchanger (NHE) is directly or indirectly responsible for most sodium bicarbonate and NaCl reabsorption by the adult proximal tubule [10, 32, 33]. The NHE secretes protons into the tubular lumen. The driving force for this process is the low intracellular sodium generated by the $Na^+/K^+$-ATPase on the basolateral membrane as depicted Fig. 1. The luminal proton titrates the filtered bicarbonate forming $H_2CO_3$, which dissociates into $CO_2+H_2O$ facilitated by carbonic anhydrase IV on the apical membrane. $CO_2$ can diffuse into the proximal tubule cell and form $H_2CO_3$, which is facilitated by carbonic anhydrase II in the cytosol. The bicarbonate formed from dissociation of $H_2CO_3$ exits the cell in a sodium-dependent manner, leaving the proton to be secreted via the apical NHE. In the adult, approximately one-third of renal acidification occurs by the $H^+$-ATPase [33, 34]. There does not appear to be any $H^+$-ATPase activity in the neonatal proximal tubule [34].

The rate of volume absorption and bicarbonate reabsorption is lower in the neonatal proximal tubule than that in the adult [13, 35]. There is a maturational increase in carbonic anhydrase II and IV and the basolateral sodium bicarbonate cotransporter that facilitates bicarbonate exit from the cell [36–39]. However, the increase in NHE activity is profound and likely accounts for most of the developmental increase in renal acidification [39–41].

There are ten NHE isoforms, but NHE3 is the predominant isoform on the apical membrane of the adult proximal tubule [42–44]. The abundance of NHE3 is far less on the brush border of the neonate compared to the adult proximal tubule [40, 45, 46]. However, unlike the adult proximal tubule where all of NHE activity could be attributed to NHE3 [43, 44], there is a discordance between NHE activity and NHE3 mRNA and protein abundance in the neonate. There is far greater NHE activity than could be explained by NHE3 alone in the neonatal proximal tubule [41]. Evidence for another proximal tubule NHE on the apical membrane was first found in $NHE3^{-/-}$ mice [47]. NHE8 was found to be this developmental NHE, which is highly expressed in neonatal proximal tubules but barely detectable in adults, as shown in Fig. 2. NHE8 was found to have significantly different properties than NHE3 in terms of its regulation and its sensitivity to amiloride analogues, which inhibit NHEs [48, 49]. Metabolic acidosis in neonates in vivo and in cells expressing NHE8 in vitro increase NHE8 activity consistent with this isoform playing an important role in neonatal proximal tubule acidification [40, 48].

The proximal tubule plays a major role in NaCl transport. Approximately two-thirds of the filtered NaCl is reabsorbed by the proximal tubule [10]. NaCl transport in the proximal tubule is in part active and mediated by the parallel operation of the apical NHE and a chloride/base exchanger [50, 51]. Thus, the parallel operation of these two transporters results in the electroneutral reabsorption of NaCl and the secretion of a hydrogen ion and a base. The nature of the base that is secreted is not clear. The base could be a hydroxyl ion resulting in the net secretion of $H^+ + OH^-$, or water. Other ions that have been postulated to be secreted in exchange for chloride include bicarbonate, formate, and oxalate [50–57]. The relative importance of these ions for the reabsorption of chloride transport in the adult and neonate is not known. The rate of active transcellular NaCl transport in neonatal proximal tubules is far less in the neonate than in the adult [55, 57]. This is due to the lower rate of the NHE as well as $Cl^-/base^-$ exchanger [55, 57].

Approximately one-third of the NaCl transport is passive and paracellular in the adult proximal tubule [58, 59]. The driving force for the paracellular reabsorption of chloride ions is the higher luminal chloride composition generated by preferential bicarbonate reabsorption in the early portion of the proximal tubule. Chloride could thus diffuse along the paracellular pathway as shown in Fig. 1. The magnitude of chloride absorption is not only dependent on the generation of a chloride concentration gradient but also the permeability properties of the paracellular pathway. There are marked differences in the permeability properties of the paracellular pathway in the neonatal and adult proximal tubule [60–64]. The neonatal proximal tubule has a lower chloride permeability and higher transepithelial resistance than that of the adult, which limits passive chloride transport in the neonate [55, 57, 65].

The tight junction between epithelial cells forms the barrier between the apical and the basolateral membrane. The fibrils in the tight junction are composed of occludin and a family of proteins called claudins, which have approximately 20 members [66, 67]. Claudins are low molecular weight proteins that have four membrane-spanning domains that join with claudins on adjoining cells. The permeability of the paracellular pathway is dependent in large part on which claudin isoforms are expressed by a nephron segment [67]. As an example, the high magnesium and calcium permeability of the paracellular

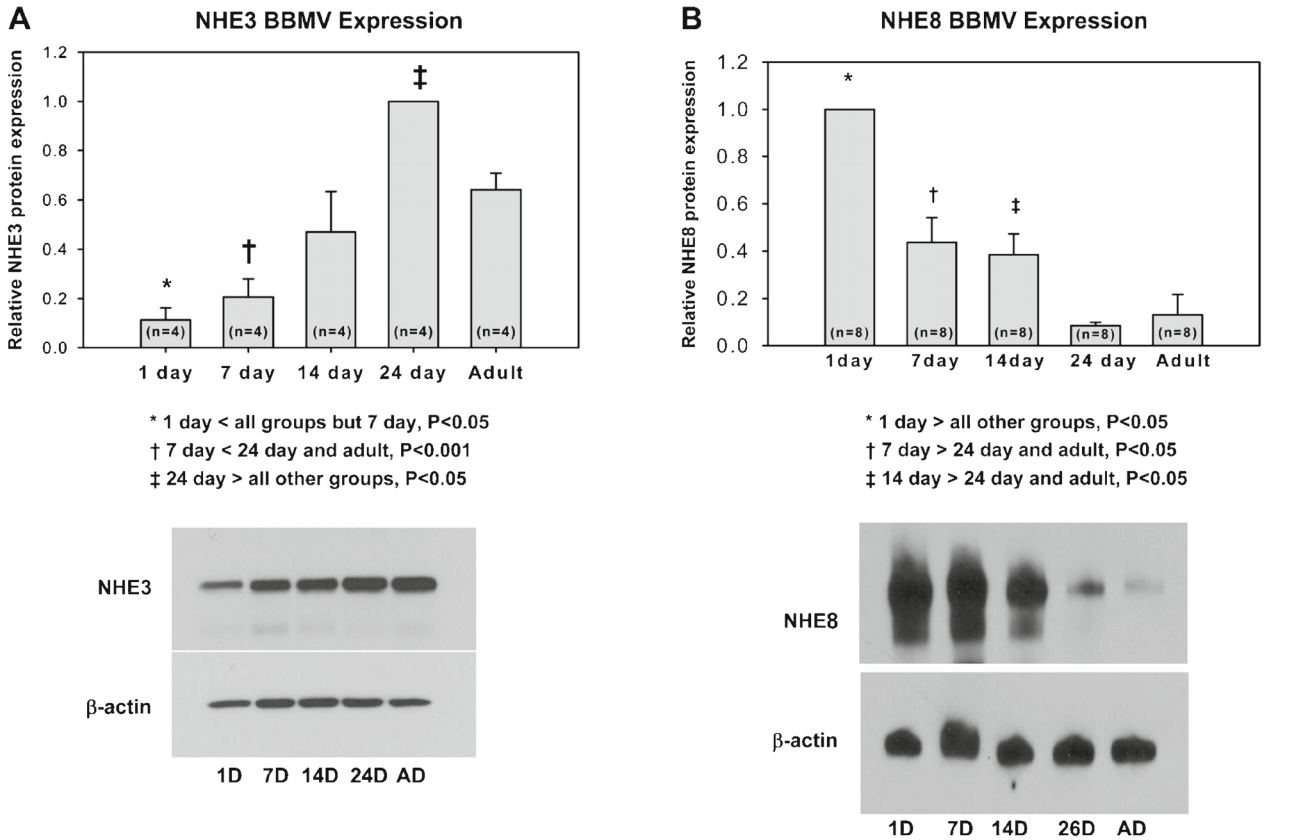


**Fig. 2** The apical protein expression of the $Na^+/H^+$ exchanger during postnatal development. As shown, NHE8 is highly expressed in the neonate while NHE3 is the predominant $Na^+/H^+$ exchanger in the adult proximal tubule. The isoform change occurs at the time of weaning and is likely mediated by the increase in thyroid hormone and glucocorticoids that occur during that time (figure reproduced from reference [40], used with permission)

pathway in the thick ascending limb is due to the expression of claudin 16 and 19 [68, 69]. Mutations in claudin 16 or 19 lead to familial hypomagnesemia with hypercalciuria [68, 70]. The adult proximal tubule expresses claudin 1, claudin 2, claudin 10a, claudin 12, and occludin. The neonatal proximal tubule not only expresses these claudin isoforms but also claudins 6, 9, and 13 [60]. Claudins 6 and 9 have been shown to increase transepithelial resistance and decrease chloride permeability when transfected into MDCK cells in vitro [71]. Thus the lower chloride permeability and higher transepithelial resistance in neonatal compared to adult proximal tubules is likely due to the expression of these two claudin isoforms.

## Phosphate transport

Phosphate is a component of nucleic acids and thus necessary for RNA and DNA synthesis. Additionally, phosphate has many important and diverse roles in intracellular signaling, enzymatic reactions, facilitating oxygen delivery, as well as being a component of bone. There are inherent developmental changes in phosphate transport from the neonate to the adult. Neonates are in positive phosphate balance, which is critical for growth and have higher serum phosphate levels compared to adults.

Adult humans ingest approximately ~1–1.5 g of phosphate every day and remain in phosphate balance. The proximal tubule is the primary site of phosphate reabsorption from the glomerular filtrate. The sodium phosphate cotransporters 2a and 2c (NaPi2a and NaPi2c) are present on the brush border of the proximal tubule and mediate reabsorption of 70–80 % of filtered phosphate. NaPi2a and NaPi2c have differing roles in phosphate reabsorption in humans and rodents. In humans, NaPi2c seems to play a major role in mediating phosphate reabsorption compared to NaPi2a, as homozygous deletion of NaPi2c causes hereditary hypophosphatemic rickets with hypercalciuria (HHRH) [72]. Patients with HHRH have hypophosphatemia, hypercalciuria, and elevated levels of 1,25 vitamin $D_3$. The role of NaPi2a in humans remains unclear. Recently, Magen et al. reported two patients with a NaPi2a mutation who had hypophosphatemia, phosphaturia, and features of Fanconi's syndrome [73].

In rodents, NaPi2a is the principal transporter responsible for reabsorption of 70 % of filtered phosphate and deletion of NaPi2a results in hypophosphatemia, phosphaturia, increased 1,25 vitamin $D_3$ levels, and skeletal abnormalities [74]. Deletion of NaPi2c in rodents did not affect serum phosphate levels, however mice lacking NaPi2c developed hypercalcemia, hypercalciuria, and elevated 1,25 vitamin $D_3$ levels [75]. Deletion of both NaPi2a and NaPi2c resulted in a more severe phenotype than that of NaPi2a null mice with regards to hypophosphatemia, phosphaturia, and skeletal mineralization defects consistent with NaPi2c playing a compensatory role in the absence of NaPi2a [76].

Neonates have a lower glomerular filtration rate (GFR) than adults; however, a reduced filtered load of phosphate is not the cause for the higher serum phosphate levels in neonates. Studies performed in 3 to 7-day newborn guinea pigs have demonstrated that for any filtered load of phosphate below the threshold maximum for phosphate, the neonate reabsorbed twice the amount of phosphate per unit mass of the kidney than the adult [77]. Similarly, growing rats had a higher rate of phosphate reabsorption (normalized for GFR) than the mature rats [78]. In humans, the fractional excretion of phosphate (FEPhos) is lower in neonates than in adults [79, 80]. Full-term neonates have a FEPhos of less than 0.2 % within the first 36 h of life, which increases to 6.5 % by 2–7 days of life [81]. This is in contrast to adults who have a FEPhos of 10–20 %.

The higher serum phosphate levels in neonates are at least in part due to increased tubular phosphate reabsorption. Brush border membrane vesicles (BBMV) from neonatal guinea pigs have a higher $V_{max}$ for phosphate uptake than adult guinea pigs [82]. Despite the higher rate of phosphate uptake by the proximal tubule, the intracellular phosphate concentration is lower in neonates than adults, suggesting that basolateral membrane phosphate transport into the blood may also be faster in neonates than adults, but this has not been studied [83, 84].

Developmental studies found that NaPi2a is initially expressed at the time of brush border development on the proximal tubule. Interestingly, there is a developmental decrease in NaPi2a protein abundance at the time of weaning when phosphate transport is very high [85]. When renal cortical mRNA from immature rats (3 weeks old) or adult rats (>12 weeks old) was injected to oocytes, phosphate uptake was higher in the oocytes with mRNA from the 3-week-old compared to the adult rat. Moreover, when mRNA derived from the kidney cortex of 3-week-old animals was depleted of NaPi2a using subtractive hybridization techniques and injected into oocytes, sodium-dependent phosphate transport was still present, while similar experiments using adult kidney mRNA abolished phosphate transport in the oocytes [86]. These data suggested the presence of another phosphate transporter responsible for maintaining the increased renal phosphate reabsorption seen at the time of weaning. Studies examining the cause for the increase in phosphate transport in weanling rats led to the discovery of NaPi2c, which is the growth-related phosphate transporter with higher expression in weaning rats than in the adult rats [87].

Parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) are phosphaturic hormones that could play a role in the higher phosphate levels in neonates. Administration of PTH to immature and adult rats decreased renal reabsorption of phosphate in both groups of rats; however, immature rats maintained a higher renal reabsorption of phosphate compared to adults [88, 89]. Furthermore, infusion of PTH into the perfusate of isolated guinea pig kidneys increased the FEPhos in adult but not neonatal kidneys [77]. Thus, these data demonstrate an attenuated response of PTH on renal phosphate transport in growing animals. A study of healthy-term infants demonstrated that intact FGF23 levels were comparable between neonates and adults despite the higher phosphate levels in neonates [90]. Whether there is a blunted response to FGF23 in neonates has not been studied.

## Thick ascending limb

The thick ascending limb reabsorbs ~25 % of the filtered NaCl and is impermeable to water, generating a tubular fluid as low as osmolality of ~50 mOsm/kg·$H_2O$. An illustration of a thick ascending limb cell is shown in Fig. 3. The generation of hypo-osmolar luminal fluid is necessary for free water excretion. NaCl reabsorbed from the thick ascending limb is also important in the generation of a hyperosmolar medullary interstitium for

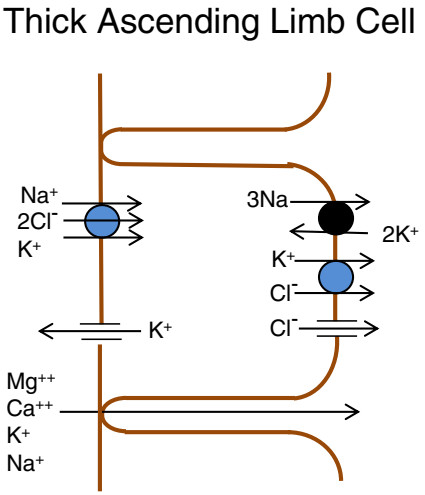


**Fig. 3** The thick ascending limb reabsorbs 25 % of the filtered NaCl. The NKCC on the apical membrane is the transporter that is inhibited by loop diuretics. The recycling of potassium across the apical potassium channel (ROMK) results in a lumen-positive potential difference. This positive lumen potential provides a driving force for passive cation absorption along the paracellular pathway. The paracellular pathway in the thick ascending limb is very permeable to cations. A mutation in transporters involved in thick ascending limb transport depicted here can cause Bartter's syndrome

urinary concentration. The luminal transporter that mediates sodium entry into the cell is the $Na^+$-$K^+$-$2Cl^-$ cotransporter (NKCC). Transport is electroneutral since two chloride ions are transported for every sodium and potassium ion [91]. This is the transporter that is inhibited by furosemide and bumetanide. There are a number of isoforms of $Na^+$-$K^+$-$2Cl^-$ cotransporter and NKCC2 is the one present in the thick ascending limb [92, 93]. Sodium exits the thick ascending limb cell via the $Na^+/K^+$-ATPase on the basolateral membrane. As in the proximal tubule, the $Na^+/K^+$-ATPase generates a low intracellular sodium concentration providing a driving force for sodium to enter the cell across the apical membrane. Chloride is transported out of the cell by ClC-Kb, a chloride channel that requires Barttin, a subunit necessary for trafficking of ClC-Kb to the basolateral membrane [94]. Potassium is recycled into the lumen via ROMK (rat outer medullary potassium channel), which generates a lumen-positive potential. This lumen-positive potential provides a driving force for passive reabsorption of cations including calcium and magnesium along the paracellular pathway. The paracellular pathway has tight junction proteins designated claudin 16 and 19, which interact to form a tight junction, which is very permeable to cations [68, 95].

Bartter's syndrome is an inherited disorder resulting from mutations in NKCC2, ROMK, ClCKb, or Barttin. There is sometimes a history of polyhydramnios and infants born with Bartter's syndrome usually present with polyuria and failure to thrive. Electrolytes reveal a hypochloremic, hypokalemic, metabolic alkalosis with hypercalciuria and nephrocalcinosis. Barttin is also expressed in the inner ear and patients with mutation in Barttin have sensorineural deafness. Patients with mutations in ROMK can develop transient hyperkalemia since ROMK is also in the collecting duct and it is not fully expressed in neonates. The calcium sensing receptor is present on the basolateral side of the thick ascending limb cell and activating mutations of this receptor have been associated with Bartter's syndrome and hypocalcemia [96, 97].

There are a number of changes that occur in the thick ascending limb during postnatal maturation. The mRNA and protein abundance of NKCC2, $Na^+/K^+$-ATPase and ROMK increase during renal development, resulting in a developmental increase in sodium reabsorption in the thick ascending limb [98–100]. Despite these maturational changes in transport, the thick ascending limb is able to dilute urine in human neonates and neonates drink mother's milk, a hypotonic fluid. Human neonates are able to excrete urine with an osmolality of ~50 mOsm/kg·$H_2O$, which is comparable to that of adults.

## Distal convoluted tubule

The distal convoluted tubule is responsible for reabsorption of 5–10 % of filtered sodium and is impermeable to water, thus maintaining the hypo-osmolar tubular fluid generated by the thick ascending limb. NaCl reabsorption primarily occurs via $Na^+$-$Cl^-$ cotransporter (NCC), which is the electroneutral transporter inhibited by thiazide diuretics [101, 102]. An illustration of a distal convoluted tubule cell is shown in Fig. 4. To a lesser extent, NaCl reabsorption occurs by parallel $Na^+$-$H^+$ exchanger (NHE2) and $HCO_3^-$-$Cl^-$ exchangers. On the basolateral membrane, similar to other parts of the nephron, $Na^+$ exit is mediated via $Na^+/K^+$-ATPase. Chloride is transported from the cell via a $K^+$-$Cl^-$ cotransporter (KCC4) and a chloride channel (ClC-K2) [103]. Potassium exits across the basolateral membrane via K channels.

Gitelman's syndrome is an autosomal recessive disorder that usually presents in late childhood or adolescence with weakness, muscle cramps, constipation, salt craving, and thirst. Patients have hypokalemic metabolic alkalosis with secondary hyperaldosteronism, hypomagnesemia, and hypocalciuria. The vast majority of the patients have a mutation in the *NCC* gene [104, 105]. A few patients have been shown to have mutations in the *ClCNKB* gene, a human ortholog of ClC-K2 [106, 107]. Patients with Gordon's syndrome (pseudohypoaldosteronism type 2 or familial hyperkalemic hypertension) have a gain of function of NCC and an inhibition in ROMK. Patients with Gordon syndrome have hypertension, hyperkalemia, low plasma renin levels, and metabolic acidosis. Mutations in *WNK1* and *WNK4* (With No Lysine kinases) are the genes responsible for Gordon's syndrome [108]. Recently, mutations in Kelch-like 3 and Cullin 3, which are involved in ubiquitination and degradation of *WNK4*, have also been shown to cause Gordon's syndrome [109, 110]. Thiazide diuretics are the treatment of choice in patients with Gordon's syndrome and the detailed description of regulation of NCC by WNKs in Gordon syndrome has been covered previously by a review in Pediatric Nephrology [108].

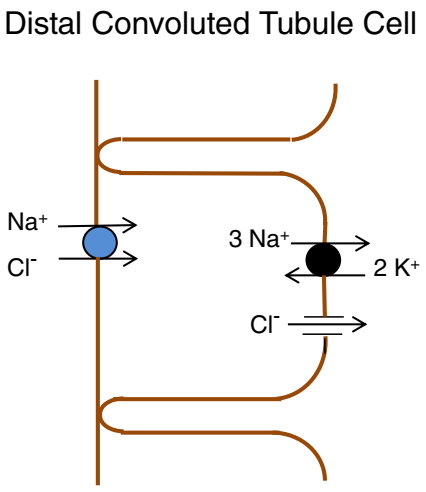


**Fig. 4** The distal convoluted tubule is responsible for 5–10 % of NaCl transport. The apical membrane NaCl cotransporter is the one inhibited by thiazide diuretics. Mutations in the NaCl cotransporter result in Gitelman's syndrome

There is limited data available on the developmental changes in solute transport in the distal convoluted tubule. Despite the decrease in sodium transport in all of the nephron segments discussed thus far, neonates are less able to excrete a sodium load compared to adults [111, 112]. A micropuncture study measured the fraction of filtered sodium remaining in the early distal tubule and late distal tubule in both volume depleted and volume expanded states [112]. In both states, a 3-week-old rat had a higher fraction of filtered sodium in the early distal tubule (keeping with decreased sodium reabsorption proximally) but had a comparable fraction of filtered sodium remaining in the late distal tubule compared to an adult rat, indicating increased distal tubule sodium reabsorption in the neonatal kidney compared to the adult.

The distal convoluted tubule is also responsible for transepithelial calcium and magnesium reabsorption via transient receptor potential vanilloid 5 (TRPV5) and transient receptor potential melastatin 6 (TRPM6), respectively [113, 114]. The distal tubule is responsible for the fine tuning of calcium and magnesium reabsorption resulting in <5 % of filtered calcium and magnesium being excreted in the urine [113]. There is not much known about the developmental changes in the expression or function of these calcium or magnesium channels.

## Urinary concentration and dilution

The thin and thick ascending limbs reabsorb solutes without water. By the end of the thick ascending limb, the urine osmolality is ~50–100 mOsm/kg·water. This is true whether the urine will be concentrated above the plasma osmolality or if the urine will be excreted at an osmolality of 50–100 mOsm/kg·water [115, 116]. There can be solute reabsorption without water in the distal convoluted tubule and collecting duct, resulting in a urine osmolality of 50 mOsm/kg·water. Whether the urine will be concentrated is dependent on an intact collecting tubule and the action of vasopressin [117]. Vasopressin is secreted if there is an increase in serum osmolality or if the effective arterial volume is very low. The adult can excrete approximately one-sixth of the glomerular filtration rate as free water (approximately 30 l/day) and thus it is virtually impossible for an adult with an intact diluting system to drink themselves into hyponatremia. On the other hand, in the presence of vasopressin, the urine osmolality can increase to 1,200 mOsm/kg·water [117]. By comparison, some desert rodents can concentrate their urine to over 3,000 mOsm/kg·water.

The human neonate can excrete urine with an osmolality of 50 mOsm/kg·water, which is fortunate, as they drink a hypotonic fluid, mother's milk [118, 119]. Nonetheless, the lower GFR in the neonate limits the ability to excrete a free water load, which is apparent when neonates are fed inappropriately diluted formula resulting in hyponatremia and seizures [120]. There is a maturational increase in the maximum urinary osmolality that can be excreted but even so a neonate is able to excrete urine with an osmolality of 600 mOsm/kg·water [121–123]. There are several reasons why a neonate cannot concentrate urine to the same extent as an adult but we will focus on maturational changes in transport.

The collecting duct responds to vasopressin by inserting aquaporin 2 containing vesicles into the apical membrane allowing water to enter the principal cell in the collecting duct. This process is dependent on cAMP, which is increased when vasopressin binds to the vasopressin 2 receptor. Water exits the cell across the basolateral membrane via aquaporin 3 and aquaporin 4. While there is a maturational increase in vasopressin receptors in the collecting duct [124], the rate-limiting step in the ability to excrete a concentrated urine appears to be the lower abundance of aquaporin 2 in the collecting duct in neonates shown in some studies [125, 126].

The level of intracellular cAMP that is generated when vasopressin binds to its receptor is lower in the neonate than in the adult [127–129]. The attenuated cAMP content is likely due to the vasopressin-induced generation of prostaglandins in the neonate, which increase phosphodiesterase activity [130, 131]. The ability of the neonatal tubule to generate cAMP in response to vasopressin is comparable to the adult when prostaglandin synthesis is inhibited [130, 131].

## Cortical collecting duct

The cortical collecting duct is responsible for the fine tuning of sodium, potassium, and acid/base transport. The collecting duct has two types of cells. The principal cell reabsorbs sodium and secretes potassium, while the intercalated cell plays a role in renal acidification. Recent studies show that there is also sodium transport in the intercalated cell, which is discussed in a recent review by Eladari et al. [132]. Examples of cortical collecting duct cells are shown in Fig. 5. Sodium is reabsorbed via the epithelial sodium channel (ENaC). ENaC has three subunits designated alpha, beta, and gamma, which are necessary for the channel to function. The trafficking of ENaC to the apical membrane is under the control of aldosterone and vasopressin [133, 134]. With insertion into the apical membrane ENaC allows sodium to traverse into the cell along the electrochemical gradient mediated by the $Na^+/K^+$-ATPase on the basolateral membrane. This results in a lumen-negative potential difference that serves as a driving force for either $K^+$ secretion through a potassium channel designated ROMK, the secretion of a proton by the neighboring intercalated cell, or the reabsorption of a chloride ion along the paracellular pathway. A gain-of-function mutation of ENaC results in Liddle's syndrome, an autosomal dominant disorder characterized by hypertension, hypokalemia, and a metabolic alkalosis [135]. A loss-of-function mutation of ENaC results in pseudohypoaldosteronism type 1,

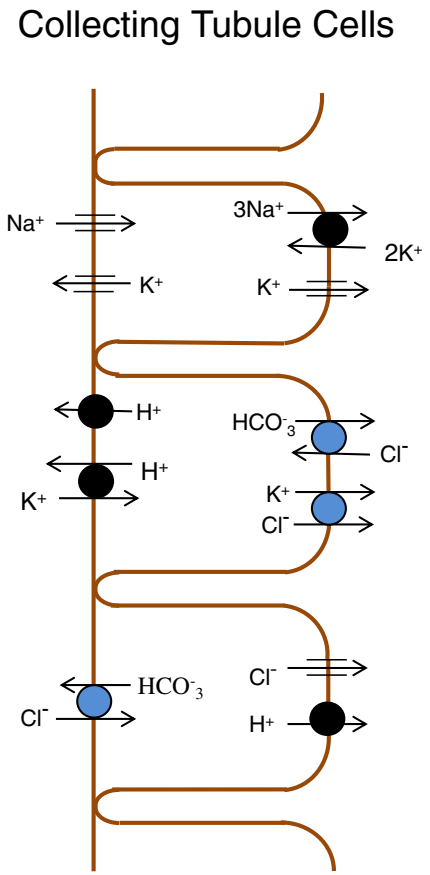


**Fig. 5** This figure depicts the three cell types in the collecting duct. The top cell is the principal cell. Sodium is absorbed across the apical membrane through a channel designated ENaC. The driving force is the basolateral $Na^+/K^+$-ATPase that lowers intracellular sodium. Sodium transport across the apical membrane results in a lumen-negative potential difference that is itself the driving force for potassium secretion through a potassium channel designated ROMK. The principal cell also expresses water channels (aquaporin 2) that are inserted into the apical membrane in response to vasopressin to increase water flow across this cell into the hypertonic medulla in order to produce concentrated urine. Below this cell is the type A intercalated cell, which plays a role in renal acidification. Both the proton pump and $H^+/K^+$-ATPase are involved in luminal proton secretion. The third cell is a type B intercalated cell, which secretes bicarbonate under conditions of a metabolic alkalosis. Note that the proton pump is on the basolateral membrane of this cell

which is characterized by hypotension, hyperkalemia, and metabolic acidosis [136].

There is postnatal maturation of the collecting duct principal cells. The rate of sodium transport and the transepithelial potential difference is less in the neonate than in the adult [137, 138]. The lower rate of sodium transport in the neonatal collecting tubule compared to the adult tubule is due to the paucity of sodium channels on the apical membrane of the neonatal collecting tubule compared to the adult, and the ones that are present are more likely to be closed not allowing sodium to enter into the cell [139]. The paucity of apical membrane sodium channels in the neonate occurs despite the fact than the mRNA abundance for all of the ENaC subunits is at the adult level by 3 days of age in the rat [140]. This indicates that there is significant posttranscriptional regulation during development that limits expression in the neonate. While aldosterone is the primary regulator of ENaC activity in the adult, there is a resistance to the action of aldosterone to increase sodium transport in the neonatal rat [140].

The intracellular potassium concentration is about 140–150 mEq/l and potassium is an essential element for growth. While the fraction of total body potassium in the extracellular fluid is very small, it is highly regulated in the adult and an increase in potassium concentration leads to an increase in aldosterone, which enhances potassium secretion by the collecting duct. Teleologically, the neonate needs to conserve potassium for growth. Several studies have shown that there is a maturational increase in the ability of the distal nephron to excrete potassium [137, 141, 142]. The maturational increase in potassium secretion by the neonatal cortical collecting duct occurs at a later time during development than that of sodium transport [137]. In the rabbit, the maturational change in potassium secretion lags behind developmental increase in collecting duct sodium transport [137].

The collecting duct has two apical potassium channels [136]. The principal cell has a potassium channel that has a high probability of being open, designated ROMK. There is also a flow-stimulated potassium channel that is activated when there is high luminal flow, which is present on principal cells but is predominantly located on intercalated cells [143, 144]. The increase in the ability to secrete potassium by the collecting tubule is due primarily to an increase in ROMK expression [145, 146]. The ability of channels to conduct ions is dependent on the number of channels present and the probability of the channels being open. During development of the collecting duct, it is the number of ROMK channels and not their open probability that limits potassium secretion [145].

The amount of potassium secretion in the adult is in part determined by flow of sodium to the distal nephron [143]. Sodium delivery in the presence of aldosterone will increase sodium absorption via ENaC, which will increase the driving force for potassium secretion by increasing the lumen-negative potential difference [136]. This flow-stimulated potassium secretion is limited in the neonate [137]. This is in part due to the limited sodium absorption by the collecting tubule of the neonate, but also because of the paucity of stretch activated maxi-K channels (also known as BK channels) [147].

The neonatal cortical collecting duct has fewer intercalated cells in the cortex than the adult, which are also histologically immature. The outer medullary collecting duct intercalated cells are more mature in appearance than in the outer cortex and are present in numbers comparable to that of the adult [148]. The intercalated cell can be of two types. The type A intercalated cell has a proton pump ($H^+$-ATPase) and as well as an $H^+/K^+$-ATPase on the apical membrane. The base that is generated from proton secretion is secreted across the

basolateral membrane by a $Cl^-/HCO^-_3$ exchanger, designated anion exchanger 1 (AE1). In the cortical collecting duct, there are also cells which have the $H^+$-ATPase on the basolateral membrane and a different $Cl^-/HCO^-_3$ exchanger, designated pendrin, on the apical membrane for base secretion if there is metabolic alkalosis. These cells are designated type B intercalated cells. The number of type A and type B intercalated cells increase in the cortical collecting duct during postnatal maturation [148–151]. The outer medullary collecting duct only has type A intercalated cells for final renal acidification.

Direct measurement of bicarbonate reabsorption has been performed in the neonatal and adult rabbit, which imbibes an alkaline mother's milk as a neonate and eats an alkaline diet as an adult. There is no net bicarbonate transport in the first several weeks of age in the cortical collecting duct. As the rabbit matures, there is net secretion of bicarbonate by the collecting duct [152]. Since there are both bicarbonate reabsorbing and bicarbonate secreting type B intercalated cells in the cortical collecting duct, it is possible that they may be functioning at an equal rate in the neonatal collecting duct resulting in no net bicarbonate transport. Removal of chloride from the basolateral side of the cell arrests the $Cl^-/HCO^-_3$ exchanger necessary for the type A cell to secrete protons into the lumen, while removal of chloride from the lumen allows one to study the type A proton secreting cell independent of the base secreting type B cell. In studies using this technique, the adult rabbit cortical collecting duct has both bicarbonate secretion and absorption with overall net bicarbonate secretion, while the neonate has little or no bicarbonate secretion and a small amount of bicarbonate absorption indicating that both acid-secreting and base secreting cells are immature at birth [152]. Consistent with the centrifugal maturation of the kidney, the outer medullary collecting duct, which secretes protons in the tubular lumen for final urinary acidification is histologically relatively mature compared to that of the cortical collecting duct [148, 150, 153]. Direct measurements of bicarbonate transport show that the rate of outer medullary collecting duct bicarbonate transport in the neonate is comparable to that of the adult [152].

## Induction of maturational changes in tubular transport

What causes the developmental changes in tubular transport? As noted, there is a developmental increase in transport for most sodium-dependent transporters along the nephron. The increase in tubular transport during development parallels the increase in GFR and there is evidence that the increase in sodium delivery can be an inductive factor inducing maturational changes in transport. An increase in apical membrane sodium transport has been shown to increase basolateral $Na^+/K^+$-ATPase [24]. However, the greatest change in transport for most sodium-dependent transporters occurs at the time of weaning. Both thyroid hormone and glucocorticoids increase at the time of weaning and there is evidence that they are responsible for the maturational change in transport of several solutes [18, 19, 154, 155].

To show that a hormone is responsible for maturation of a developmental process, the change in that process should be concordant with the change in concentration of that hormone. In addition, administration of the hormone before the normal maturational change should result in a premature change in the process being studied and prevention of the maturational change if the hormone should prevent that normal maturational change in the process from occurring. Finally, the hormone should be able to effect the change in the process in vitro. As an example of how glucocorticoids affect tubular development, let us examine the $Na^+/H^+$ exchanger NHE3 where all the criteria for demonstrating the importance in renal maturation have been fulfilled. First, as shown in Fig. 2, the increase in NHE3 occurs at about the time of weaning, which is also the time when there is a decrease in NHE8 [40, 46]. Prenatal administration of dexamethasone increases the rate of neonatal proximal convoluted tubule bicarbonate absorption to rates measured in adults [35]. Dexamethasone has a direct epithelial action to increase NHE3 activity in OKP cells (Opossum Kidney Proximal Tubular Cells) in vitro by increasing gene transcription [156, 157]. Neonatal adrenalectomy partially prevents the developmental increase in brush border membrane NHE3 protein abundance and NHE activity but has no effect on NHE3 mRNA abundance [158]. However, preventing the developmental increase in both thyroid hormone and glucocorticoids totally prevents the increase in NHE3 mRNA, brush border membrane protein, and NHE activity [159]. In addition, glucocorticoids decrease the expression of brush border membrane NHE8 in neonates and decrease NHE8 transporter activity in vitro [160]. Thus, glucocorticoids are likely an important factor in the maturational increase in NHE3 and may play a role in the maturational decrease in NHE8.

There is evidence that glucocorticoids affect the maturation of multiple other transporters. Administration of glucocorticoids to rat neonates prematurely increases $Na^+/K^+$-ATPase mRNA abundance and activity [17, 22, 161] and thus could increase sodium transport in multiple nephron segments. Glucocorticoid administration to neonates results in a decrease in the rate of phosphate transport as well as a decrease in apical membrane phosphate transporter abundance [162, 163]. Administration of dexamethasone to neonatal rats increases NKCC and ROMK mRNA and protein abundance in the thick ascending limb [98, 126]. In addition, administration of dexamethasone increases aquaporin 2 mRNA and protein expression and the urinary concentrating ability of neonatal rats [98, 126].

Serum thyroid hormone levels increase threefold at the time of weaning and thyroid hormone has been shown to have a role in the isoform switch from NHE8 to NHE3 [19]. Administration of thyroid hormone to neonates increases brush border membrane NHE activity, while maintaining a low

thyroid hormone during development prevents the maturational increase in NHE activity [154]. Thyroid hormone has opposing effects on NHE3 and NHE8 expression. Administration of thyroid hormone to neonatal rats before the developmental isoform switch results in an increase in NHE3 and decrease in NHE8 protein expression [164]. Preventing the developmental increase in thyroid hormone prevents the developmental increase in NHE3 and decrease in NHE8 [159]. Thyroid hormone has a direct epithelial effect in vitro to increase NHE3 protein abundance and NHE3 activity in OKP cells that express NHE3 [165], while thyroid hormone decreases NHE8 protein abundance and NHE activity in NRK cells that express NHE8 [164]. The chloride base exchanger is also affected by the developmental change in thyroid hormone affecting active NaCl transport [57]. Thyroid hormone also affects the maturation of passive transport by increasing the chloride permeability of the paracellular pathway [57].

In summary, this review covers developmental changes that occur in tubular transport along the nephron. In addition to changes in transporter abundance and isoform changes for some transporters, most transporters are regulated by hormones and other factors such as pH, electrolytes, and renal nerves. The concentration of many hormones that affect transport, their receptor abundance and signal transduction pathways can undergo developmental changes as well, which is a topic beyond the scope of the present review. In spite of all these developmental changes, the kidney is able to alter transport appropriately to buffer changes that occur in the extracellular fluid.

## Summary points

- There is a significant increase in the glomerular filtration rate during postnatal development, which is paralleled by an increase in tubular transport.
- In addition to a maturational increase in transporter abundance, there are isoform changes for some transporters during postnatal maturation.
- The developmental increase in serum glucocorticoids and thyroid hormone that occurs at the time of weaning is an important factor inducing developmental changes in several transporters.

## Multiple choice questions (answers are provided following the reference list)

1. Which of the following statements about the glomerular filtration rate is true:

   A. The postnatal increase in glomerular filtration rate is due predominantly due to the increase in glomerular capillary surface area.
   B. Glomerulogenesis is always complete by time of birth.
   C. When corrected for body surface area, the glomerular filtration rate remains constant after birth.
   D. The glomerular filtrate of the adult is an ultrafiltrate of plasma unlike that of the neonate.
   E. Superficial nephrons are formed before juxtamedullary nephrons due to centrifugal pattern of nephron maturation.

2. Which statement about proximal tubule transport is correct?

   A. While there is substantial reabsorption of solutes, the composition of the luminal fluid remains constant along the proximal tubule.
   B. There is an isoform switch of the $Na^+/H^+$ exchanger from NHE8 to NHE3 during postnatal development.
   C. PTH is responsible for the developmental increase in proximal tubular phosphate transport.
   D. The main driving force for solute transport is the apical membrane $Na^+/K^+$-ATPase pump.
   E. The osmolality of the luminal fluid of the late proximal tubular fluid is higher than that in the peritubular capillaries.

3. Which of the following statements is true about the collecting duct:

   A. Transport by the cortical collecting duct is predominantly regulated by vasopressin.
   B. The reabsorption of sodium across the apical membrane is via an electroneutral mechanism.
   C. There is a maturational increase in both the apical epithelial sodium channel and potassium channel during post natal development.
   D. Sodium transport is mediated by an aldosterone-sensitive channel designated ROMK.
   E. The low intracellular potassium concentration in this segment is due to the basolateral $Na^+/K^+$-ATPase.

4. Which of the following is true regarding urinary dilution in the neonate:

   A. Urinary dilution occurs in the collecting duct.
   B. The diluting segment is permeable to water in the neonate compromising the diluting capacity.
   C. A neonate cannot drink enough free water to develop hyponatremia.
   D. The neonate can dilute urine to 50 mOsm/kg·$H_2O$.
   E. Adults with normal diluting capacity can excrete 30 % of their glomerular filtrate as free water.

5. Which of the following is true regarding the developmental changes in urinary concentrating ability:

   A. The term neonate can concentrate urine to 600 mOsm/kg·$H_2O$.
   B. The final urine osmolality in the neonate is dependent on aquaporin 1 trafficking to the apical membrane.

C. The neonate cannot concentrate urine above the plasma osmolality.
D. Unlike adults, vasopressin does not regulate urine osmolality in the premature neonate.
E. The final urine osmolality is due entirely to the osmolality of the interstitial fluid.

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## Answers

1. A
2. B
3. C
4. D
5. A