Ontogeny of Renal Sodium Transport

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One of the main functions of the adult kidney is to maintain a constant extracellular fluid balance. The adult kidney does this, by and large, by filtering a massive quantity of fluid and reabsorbing the solutes needed to maintain volume and electrolyte homeostasis, while leaving the waste products to be excreted in the urine. One of the most precisely regulated functions of the adult kidney is to maintain sodium balance. The challenge of the neonatal kidney is even greater. It must maintain a positive salt balance for growth while the neonate is fed a diet that is very low in sodium. This review focuses on how the neonatal kidney reabsorbs NaCl with a special emphasis on the differences between the neonatal and adult kidney.

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Of the 150 L the adult kidney filters a day, only ~1% is excreted in the urine. Thus, one of the primary roles of the renal tubules is to reabsorb most of the salt and water filtered by the glomerulus. The problem is much more complicated as the kidney has to maintain NaCl balance in the face of a variable salt intake. If an adult changes his diet from a moderate NaCl intake to a diet rich in pepperoni pizzas the kidney will excrete this salt load to maintain salt balance. If NaCl output did not match NaCl intake hypertension, edema and congestive heart failure would be the result of this dietary indiscretion. On the other hand, the kidney can adapt to a low sodium intake or states of volume depletion to excrete almost no sodium. This balance of sodium intake to excretion maintains a constant extracellular fluid balance.

Unlike the adult who has a variable salt intake, the neonate only drinks milk, a fluid that is very low in sodium and chloride. While a major task of the adult kidney is to maintain salt balance, this would be ill suited for a neonate that must constantly be in positive NaCl balance in order to grow. Thus, the neonatal kidney is challenged to maintain a positive salt balance in spite of the fact that the dietary intake of salt is extremely low. The difference in the neonatal and adult kidney is exemplified by an experiment where neonatal and adult dogs were both given an isotonic NaCl load equal to 10% of their weight.1 While the adult dog excreted 50% of the sodium load within 2 hours, the newborn dog had excreted only 10% by that time.1

Sodium handling is quite different in extremely premature neonates. The challenge of reabsorbing all of the filtered sodium is not met in these neonates, let alone maintaining positive sodium and chloride balance for growth. The renal salt wasting is due to tubular immaturity, which results in hyponatremia unless extra sodium is provided or unless the neonate is fluid restricted.

How does the neonatal kidney maintain positive salt balance in spite of the fact that mother’s milk is so low in sodium? The kidney of a term infant only filters one twenty-fifth the volume of fluid as that of the adult. The glomerular filtration rate is much lower than that of the adult even if one corrects for the body surface area. The low glomerular filtration rate makes the job of NaCl reabsorption a lot easier because less salt is delivered to the tubules. None-the-less the renal tubules of the neonate must reabsorb almost all of the filtered salt and water. In this short review, the mechanisms of renal salt reabsorption are discussed with an emphasis on the differences between the neonatal and adult kidney. As a general rule of thumb, almost all transport is secondary to the sodium pump (Na+/H+-ATPase) on the basolateral membrane. The Na+/H+-ATPase transports 3 sodium ions out of the cell in exchange for 2 potassium ions into the cell. This results in a cell with sodium con-
centration approximately one tenth that of the blood and with a potential difference of -60 mV. Most solute transport, either directly or indirectly, uses this huge electrochemical gradient as the driving force for solute entry. Most solute exit across the basolateral membrane is via passive diffusion. The transporters responsible for NaCl transport along the nephron are shown in Figure 1.

**Proximal Tubule Transport**

The proximal tubule receives an ultrafiltrate of plasma and reabsorbs all the filtered glucose and amino acids, three quarters of the filtered bicarbonate, and two thirds of the filtered chloride. There are several different mechanisms for the reabsorption of NaCl by the proximal tubule. The early proximal tubule preferentially reabsorbs glucose, amino acids, and bicarbonate over chloride ions. This leaves the late proximal tubule luminal fluid without organic solutes and with a very low concentration of bicarbonate. Sodium and chloride are essentially the only solutes in the lumen of the distal half of the proximal tubule.

The proximal tubule is the hardest working tubular segment, yet it does try to get as much NaCl transport reabsorption as possible while doing the minimum amount of work. The trick that the proximal tubule uses is to separate the reabsorption of solutes into the 2 phases described above. During the first phase where all the glucose and amino acids are reabsorbed, solute entry into the proximal tubule cell is via sodium-dependent transporters. The reabsorption of the positively charged sodium along with glucose or amino acids leaves a lumen negative transepithelial potential difference. This negative potential provides a driving force for passive chloride transport across the paracellular pathway. Thus for each glucose molecule reabsorbed

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**Figure 1.** The nephron with the transporters responsible for sodium transport in the various nephron segments.
one also gets the reabsorption of a Na and Cl molecule.

The vast majority of NaCl transport occurs in the late proximal tubule where in the adult segment half of NaCl transport is active and transcellular and half is passive and paracellular.\(^{4,6}\) The active component of NaCl transport is mediated by the parallel operation of a Na\(^+\)/H\(^+\) exchanger and a Cl\(^-\)/OH\(^-\) exchanger.\(^{6,10}\) When both of these transporters turn over, we have the net reabsorption of a sodium and a chloride ion and the secretion of a H\(^+\) and an OH \(^-\) ion or simply a water molecule. The Na\(^+\)/H\(^+\) exchanger actually plays a role not only in sodium reabsorption but it is the primary mechanism for luminal proton secretion and thus the reabsorption of bicarbonate in the early proximal tubule.

As mentioned above the preferential reabsorption of organic solutes and bicarbonate in the initial phase of proximal tubule reabsorption results in a luminal fluid that is essentially composed of NaCl. This provides another way of getting something for nothing. In the adult proximal tubule, the chloride permeability of the tight junction is very high.\(^{11}\) Because the luminal chloride concentration is higher than that in the peritubular plasma, the chloride concentration gradient provides a driving force for passive chloride diffusion from the lumen across the tight junction into the peritubular plasma. The paracellular diffusion of the negatively charged chloride results in a lumen positive potential difference, which provides the driving force for passive paracellular NaCl transport.\(^{3}\)

Well, how about the neonatal proximal tubule? There are several important differences in transport between the adult and the neonate. The overall theme, not only in the proximal tubule, but down the entire nephron is that the transporters responsible for solute absorption are exactly the same, but the abundance is lower in the neonatal tubule. This is true for the first part of NaCl transport as well as active NaCl transport where the apical Na\(^+\)/H\(^+\) exchanger and Cl\(^-\)/OH\(^-\) exchangers are in lower abundance,\(^{5,12-14}\) as well as the basolateral Na\(^+\)-K\(^+\)-ATPase and the basolateral chloride transporters.\(^{15,16}\) This is no tragedy because the amount of fluid filtered and delivered to the tubules is much less in the neonate. Studies have shown that the fraction of the total fluid reabsorbed in the proximal tubule is the same in the neonate as the adult proximal tubule.

There are surprising differences in the fraction of NaCl transported across the paracellular pathway in the neonatal proximal tubule compared to the adult proximal tubule. Although half of chloride transport is passive and paracellular in the adult, because of the concentration gradient and the high chloride permeability in the adult segment, the neonatal proximal tubule has no passive chloride transport.\(^{11}\) While a gradient develops favoring passive diffusion in the neonatal tubule as it does in the adult, the neonatal proximal tubule is completely impermeable to chloride.\(^{11}\)

The above issues raise the question as to what causes the maturational changes in transporter abundance and paracellular permeability. There are a number of hormonal changes that occur during the postnatal period. The neonate has low serum levels of glucocorticoids and thyroid hormone that increase to adult levels around the time of weaning in most animals. As an example of how the neonatal transporters change, the authors discuss the apical Na\(^+\)/H\(^+\) exchanger because this is an important transporter and we know the most about how this changes during development. The newborn kidney has extremely low Na\(^+\)/H\(^+\) antiporter activity compared to adults.\(^{6,10,14,17-20}\) If one adrenalectomizes a neonate to prevent the maturational increase in glucocorticoids, the postnatal increase in Na\(^+\)/H\(^+\) exchanger activity, mRNA and brush border membrane protein abundance is markedly attenuated.\(^{21}\) On the other hand, if one administers glucocorticoids to the fetus and studies the neonate after delivery, the rate and abundance of the Na\(^+\)/H\(^+\) exchanger is comparable to that of the adult tubule.\(^{14,19}\)

Thus, glucocorticoids appear to be the main factor causing the maturation of not only this but most transporters along the nephron.

The factors causing the maturational changes that occur in the paracellular pathway are quite different. The tight junction is made up of proteins that shake hands with the neighboring cells to cause the ion selective and restrictive permeability barrier. The changes in abundance in tight junction proteins during postnatal maturational cause the change in the permeability barrier to chloride transport seen in the proximal tubule. It appears that the maturational change in thyroid hormone causes the change in the permeability properties of the proximal tubule to chloride ions.\(^{6}\) Animals made hypothyroid at
birth never increase their proximal tubule para-
cellular permeability to chloride ions, whereas
 neonates that are administered thyroid hormone have a paracellular chloride permeability comparable to that of adults.

Finally, we must discuss water transport across
the proximal tubule. The glomerulus produces
an ultrafiltrate of plasma with an osmolality the
same as that of blood. By the end of the proximal
tubule most of the glomerular ultrafiltrate has
been absorbed yet the osmolality of the tubular
fluid has not changed. Thus, the proximal
tubule must be very permeable to water. The
adult tubule transports water across the apical
and basolateral membranes through water chan-
nels called aquaporins. The neonatal proximal
tubule is as permeable to water as the adult
segment, despite the fact that the abundance of
aquaporin water channels is very low. Water
transport in the neonatal tubule is via a non-
aquaporin mediated mechanism, likely via other
transporters promiscuous for water, the paracel-
lular pathway, or a more water permeable cell
membrane. Whereas the apical and basolateral
membrane are less permeable to water in the
neonatal segment, the cytoplasm of the neonate
allows water to pass with less restriction than the
adult segment.\textsuperscript{22-28} The postnatal increase in
aquaporin expression is also mediated by glu-
cocorticoids.\textsuperscript{23}

**Thick Ascending Limb and Distal
Convoluted Tubule**

Because the neonate drinks a hypotonic fluid, the
neonatal kidney must have a way of produc-
ing dilute urine. The neonate can actually dilute
urine to the same minimal osmolality as that of
an adult, 50 mOsm/kg water. To do this there
must be a nephron segments that reabsorb salt
but are impermeable to water. These segments
are the thick ascending limb and distal convo-
luted tubule that reabsorb 25% and 5% of the
filtered sodium, respectively.

The thick ascending limb reabsorbs sodium
via an electroneutral sodium-potassium-2 chlo-ide cotransporter (NKCC2). This is the trans-
porter that is inhibited by furosemide and bu-
metanide. This is also one the transporters that
has been found to be mutated in Bartter’s Syn-
drome along with the basolateral chloride chan-
nel and luminal potassium channel.\textsuperscript{29-33} This
transporter is electroneutral, but because of the
apical membrane potassium channel, potassium
diffuses back from the cell into the tubular lu-
men. This leaves the tubular lumen with a large
lumen positive potential difference. The tight
junction of the thick ascending limb is very per-
meable to cations and the positive potential dif-
ference provides a driving force for the paracel-
lular absorption of calcium, magnesium, potassium, and sodium. This is clinically signifi-
cant since administration of furosemide will re-
sult in an increase in not only sodium excretion,
but also magnesium and calcium excretion. The
hypercalciuria that results from furosemide ad-
mistration is the reason that neonates develop
nephrocalcinosis if treated for extended periods
of time with furosemide. On the other hand, the
fact that it inhibits calcium absorption makes it a
useful drug to treat hypercalcemia in a well-
hydrated patient.

The distal convoluted tubule reabsorbs so-
dium chloride via an electroneutral NaCl co-
transporter. This cotransporter results in the re-
absorption of 5% of the filtered NaCl and is the
site of action of the thiazide diuretics. Gitel-
man’s syndrome, an autosomal recessive salt
wasting disease, is caused by a mutation of this
transporter.\textsuperscript{32-36} Patients with this disorder have
a hypokalemic alkalosis, as with Bartter’s syn-
drome, but patients with Gitelman’s syndrome
are less severely affected. They are distinguished
from Bartter’s Syndrome by presentation out-
side of the neonatal period, low calcium excre-
tion rates, and profound hypomagnesemia. Thi-
azide diuretics result in an increase in calcium
reabsorption in this segment and are thus clin-
ically useful as a diuretic in neonates to prevent
nephrocalcinosis. Although it is not completely
clear how thiazides increase calcium absorption,
one theory is that by decreasing NaCl absorp-
tion they increase chloride entry across the basolat-
eral membrane via passive diffusion resulting in
a more negative transcellular potential differ-
ence. This negative potential increases the driv-
ing force for calcium transport into the cell, the
rate-limiting step in calcium absorption.

All of the transporters in the thick ascending
limb and distal convoluted tubule, that have
been studied, are in lower abundance than that
of the mature segment.\textsuperscript{15,37-39} The maturation of
the Na\textsuperscript{+}-K\textsuperscript{+}-ATPase in the thick ascending limb
is mediated by perinatal increase in glucocorti-
coids.\textsuperscript{38} While all of the transporters are in lower
abundance, one of the primary function of this
segment is to reabsorb salt without water and generate a dilute urine so that infants do not develop hyponatremia when drinking mothers milk; a function that these segments perform adequately with the relatively small amount of sodium delivered to them.

**Collecting Duct**

The collecting duct reabsorbs only 1% to 3% of the filtered sodium but nonetheless plays a vital role in sodium homeostasis because the final modulation of sodium reabsorption is performed here. As is shown in Figure 1, the reabsorption of sodium is via a sodium channel in principal cells in the collecting tubule. The reabsorption of sodium in this segment results in a large lumen negative potential difference that results in either the secretion of potassium, reabsorption of chloride through the paracellular pathway, or the secretion of a proton. The driving force for sodium absorption is the basolateral Na⁺-K⁺-ATPase. All of the aforementioned transporters in this segment are regulated by aldosterone. This is why aldosterone deficiency or damage to the collecting tubule from obstructive uropathy results in hyperkalemic metabolic acidosis (type IV RTA), while hyperaldosteronism results in hypertension associated with hypokalemic metabolic alkalosis.

The sodium channel in this segment has been designated ENaC. Its surface expression is increased in Liddle’s syndrome, which results in hypertension associated with hypokalemic alkalosis, but low serum aldosterone levels. A defect in either the aldosterone receptor or the sodium channel itself leads to pseudohypoaldosteronism. Neonates with the channel defect are more severely affected than those with the aldosterone receptor mutation and have respiratory distress as neonates, since the reabsorption of perinatal pulmonary fluid is partially dependent on the pulmonary ENaC function. In addition the activity of the basolateral Na⁺-K⁺-ATPase is also lower in the neonatal cortical collecting tubule than in the adult segment.

**References**