Introduction to Kidney Tubule Anatomy

The kidneys play critical roles in the regulation of numerous biochemical processes well beyond the simple excretion of metabolic waste products. One of the most important functions of the kidneys is to regulate water and electrolyte balances which ensures homeostatic composition of body fluids allowing for normal functioning of cells. In addition to water and electrolyte balance the kidneys regulate acid-base balance, regulate arterial pressures, control body fluid osmolarity, and allow for excretion of metabolic waste products and xenobiotic substances. The kidneys are also involved in the synthesis of numerous hormones including peptide hormones such as erythropoietin (EPO), several steroid hormones, and catecholamine hormones. In addition to synthesis of hormones the kidneys also function in the regulation of the production of other hormones such as calcitriol (1,25-dihydroxyvitamin D3) and angiotensin II. The synthesis of angiotensin II is regulated by the kidney through the synthesis and release of the hormone/enzyme renin. Renin is produced by a specialized smooth muscle cell present in the walls of the afferent arterioles within the glomerulus. These renin secreting cells are called juxtaglomerular cells, JG cells (also called granular cells). The kidneys are also critical in metabolic and energy regulation through their ability to contribute to endogenous glucose production via gluconeogenesis. In order to accomplish these critical functions the kidneys are anatomically organized into substructures that are designed to allow for highly efficient filtration of components in the blood and to reabsorb components from the future urine.

Within the context of kidney anatomy there are two major organizational domains called the cortex and the medulla. The cortex represents the outer region and the medulla the inner region of each kidney. Several cell types within the cortex are responsible for the synthesis of the glucocorticoids, the mineralocorticoids, and the androgenic steroid hormones. The renal medulla is divided into cone shaped domains, 8-10 in each kidney, that are called the renal pyramids. Within the medulla there are specialized cells, medullary chromaffin cells, that synthesize the catecholamines, epinephrine and norepinephrine. The adrenal medullary chromaffin cells are functionally equivalent to postganglionic neurons of the sympathetic nervous system and in response to acetylcholine release from sympathetic preganglionic neurons theses cells release epinephrine and norepinephrine into the circulation. The renal pyramids of the medulla terminate in the papilla which project into a funnel-shaped domain called the renal pelvis. The renal pelvis consists of minor and major calyces that collect urine from each of the papilla.

Within the renal pyramids, spanning across the outer border between the cortex and the medulla, are the blood filtering components of the kidney. These anatomical structures are called nephrons and each human kidney contains from 800,000 to 1,000,000 nephrons. Blood flow into and out of each nephron involves the arcuate artery and arcuate vein. Each nephron initiates at a compact cluster (tuft) called the glomerulus that is formed from the afferent arterioles that branch off of the arcuate artery. Each tuft of afferent arteriole is covered by epithelial cells

which encase the glomerulus in what is called Bowman's capsule. Blood flowing through the glomerular arteries is filtered by the epithelial cells that form Bowman's capsule. The vasculature that exits from Bowman's capsule is called the efferent arteriole which becomes the peritubular capillaries and then on the venous side becomes the renal vein.

The filtrate from Bowman's capsule then flows through the complex structurally and functionally distinct regions of the nephron commonly referred to in its entirety as the renal tubule or the tubular filtration system. The renal tubule is composed of at least 14 segments which contain at least 16 distinct epithelial cell types. From the glomerulus, the renal tubule anatomy is structurally and functionally characterized by the proximal convouluted tubule (PCT), the proximal straight tubule (PST), the descending thin limb (DTL) of the loop of Henle, the ascending thin limb (ATL) of the loop of Henle, the thick ascending limb (TAL) of the loop of Henle, the macula densa (MD) , the distal convoluted tubule (DCT), the connecting tubule (CNT), the cortical collecting ducts, the outer medullary collecting duct, and the inner medullary collecting duct. Each of these renal tubule regions consist of specialized epithelial cells whose transport functions are outlined in the sections that follow.

Following the epithelial tubular structure of Bowman's capsule, the filtrate enters the proximal tubule which resides within the cortical tissue of the kidney. The proximal tubule is anatomically divided into the proximal convoluted tubule (PCT; also known as *pars convoluta*) and the proximal straight tubule (PST; also known as *pars recta*). Additional complexity of the proximal tubule results from the ultrastructural organization of the cells along its length which are designated as the S1, S2, and S3 segments with S1 being next to the glomerulus and S3 farthest from the glomerulus and often being associated with the small thick portion at the beginning of the descending limb of the loop of Henle. The cellular complexity of the proximal tubule also differs, being highest in the S1 segment and lowest in the S3 segment.

Following the proximal tubule the filtrate flows into the loop of Henle which penetrates into the renal medullary tissue. The loop of Henle consists of a descending and an ascending limb. Both limbs of the loop of Henle have thick and thin regions where the thick segment of the descending limb is small in comparison to the thin segment. The thin and thick segments of the ascending limb are approximately equivalent in length.

Following the loop of Henle the nephron re-enters the renal cortical tissue where a short segment, that contains a cluster of specialized epithelial cells, forms what is called the macula densa. After leaving the macula densa the filtered fluid enters the tubular structure called the distal convoluted tubule (DCT). The DCT is followed by the connecting tubule and then the cortical collecting tubule. Along the cortical collecting tubule are several cortical collecting ducts that connect numerous nephrons together within a renal pyramid. The cortical collecting ducts combine as the tubule re-enters the renal

medullary tissue and at this point the tubule is referred to as the medullary collecting tubule. The medullary collecting tubule becomes the medullary collecting ducts which merge to form progressively larger ducts that eventually empty the resulting urine into the renal pelvis through the renal papillae. Approximately 3,000-4,000 individual nephrons eventually combine together in one of these large medullary collecting ducts.

The various epithelial cells along the length of the renal tubular filtration systems have distinct functions that are dictated by the unique organization of their basolateral and apical membranes. The cells of the glomerulus are the podocytes, parietal epithelial cells, mesangial cells, and glomerular endothelial cells. Proximal convoluted tubule epithelial cells are termed PCT cells and proximal straight tubules epithelial cells are PST cells. The descending thin limb of the loop of Henle contains three epithelial cells types identified as DTL1, DTL2, and DTL3. The epithelial cells of the ascending thin limb of the loop of Henle are termed ATL cells. The thick ascending limb of the loop of Henle contains medullary (MTAL) and cortical (CTAL) epithelial cells. The division of the distal convoluted tubule is defined by DCT1 and DCT2 cells. The connecting tubule contains two distinct types of epithelial cell termed type B intercalated cells and the non-A, non-B intercalated cells. The cortical collecting duct contains three types of epithelial cell termed principal cells, type A intercalated cells, and type B intercalated cells. The outer medullary collecting duct epithelial cells include principal cells and type A intercalated cells.

The basolateral membranes of the renal tubular epithelial cells are in contact with the blood of the renal capillaries and as such can absorb electrolytes and/or compounds from the blood into the cell through the actions of specific transporter proteins and transporter complexes. These transporters are referred to as basolateral uptake transporters. In addition, the basolateral membranes can efflux electrolytes and compounds back into the blood through the actions of different transporter proteins and complexes. These transporters are referred to as basolateral efflux transporters. Similarly, the apical membranes of renal epithelial cells can efflux (apical efflux transporters) electrolytes or compounds from the cell into the renal filtrate (future urinary fluid) or reabsorb (apical uptake transporters) electrolytes or compounds from the renal filtrate through the actions of various transporter proteins or transporter complexes. Renal epithelial cells express a large number of different genes encoding the various types of basolateral and apical membrane transporter proteins and complexes.

Bowman's Capsule and Glomerulus

As blood enters the capillaries that form the tuft of the glomerulus of a nephron it is filtered into the epithelial cells that form Bowman's capsule. Although the filtration capacity within the glomerulus is quite high, on the order of 180 liters of vascular fluid per day between both kidneys, the vast majority of that filtrate is reabsorbed as the fluid progresses along the nephrons. The capillaries of the glomerulus are relatively impermeable to proteins and

constituents of cells such that the composition of the glomerular filtrate is similar to that of the plasma. The exceptions to this are plasma constituents that are bound to protein and thus not filtered into the cells of Bowman's capsule. Although most plasma electrolytes are readily filtered in the glomerulus, almost half of the calcium in the plasma is bound to protein and, therefore, not filtered. The rate of filtration of the blood that occurs within the glomerulus is called the glomerular filtration rate, GFR. The GFR is approximately 20% of renal blood flow in a healthy kidney. Overall GFR is determined by the capillary filtration coefficient and the balance of hydrostatic and osmotic forces being exerted across the capillary membrane. The high filtration capacity of glomerular capillaries is primarily due to the fact that the endothelial cell lining of these vessels is punctuated by thousands of fenestrae (holes) similar to the capillaries of the liver vasculature.

Tubular Reabsorption and Excretion

The glomerular filtrate exits Bowman's capsule to begin its journey through the specialized tubule anatomy of the nephron. All along the nephron from the proximal tubule to the papillary ducts the composition of the original glomerular filtrate changes due to the processes of efflux and reabsorption. Although, as discussed in more detail below, there are numerous highly specialized transporters distributed in the membranes of the various different tubular epithelial cells, the generalities are outline briefly here. As indicated above, the filtrate enters the proximal tubule where a large portion is reabsorbed which includes water, ions (e.g. Na^+, Cl^-, Ca^{2+}, HCO_3^-, K^+, and phosphate), and all organic nutrients, particularly glucose and amino acids. Excretion of organic acids and bases and hydrogen ion (H^+) also occurs within the proximal tubule. The filtrate then enters the loop of Henle, first at the descending limb and then the ascending limb. During transit down the descending limb more water is reabsorbed and up the ascending limb ions (e.g. Na^+, Cl^-, K^+, Ca^{2+}, Mg^{2+}, and HCO_3^-) and other solutes are reabsorbed while H^+ is excreted. Within the next segment, the distal convoluted tubule (DCT), ions, acids, xenobiotics such as drugs and toxins are effluxed into the tubular lumen while some more water is reabsorbed. Within the distal convoluted tubule Na^+, Cl–, Ca2+, and phosphate reabsorption occurs under the influence of hormones such as aldosterone, parathyroid hormone, and calcitriol. Sodium and chloride reabsorption within the DCT is also controlled by a family of kinases called the WNK kinases as discussed in detail below. Within the DCT and the cortical collecting tubules there are specialized cells called principal cells and intercalated cells. There are two types of intercalated cells identified as type A (alpha) and type B (beta). Principal cells reabsorb Na+ and excrete K+. Principal cells are the major cell types that respond to the actions of aldosterone. Type A intercalated cells reabsorb K+ and HCO3– and excrete H+. Type B intercalated cells function in opposition to type A cells such that they secrete HCO3– and reabsorb H+. The differences in function between type A and type B intercalated cells is due, in part, to the opposing distributions of various transporter proteins which, for example, places a particular transporter in the apical membrane of a

type A cell and the same transporter in the basolateral membrane of a type B cell. Within the medullary collecting duct Na+, Cl–, HCO3–, and urea are reabsorbed while H+ is excreted. Water reabsorption in the medullary collecting ducts is controlled by vasopressin (anti-diuretic hormone).

Introduction to Transporter Systems of the Nephron

Proteins and protein complexes that are involved in the transport of ions and solutes across renal tubule epithelial cell membranes have an historical naming system and conventional naming system. Many of the transporters of renal tubules are not unique to the kidney but are also prominently expressed in intestinal epithelial cells and in the liver, and in many cases at some level in several other tissues as well. Renal epithelial cell transporters are also expressed on specific sides of the plasma membranes of these cells such that certain transporters are only found on the blood side membrane (basolateral) while others are found only on the lumenal side membrane (apical).

Most often the functional nomenclature for renal transporters can be a bit confusing as well since a common theme is to indicate a transporter present on the basolateral (blood side) membrane is functioning as an excretion transporter while a transporter found in the apical (lumenal side) membrane is functioning as an uptake or reabsorption transporter. More specifically the terms uptake transporter and efflux transporter are best used to describe the functions of membrane transporters particularly in the context of renal tubular transport systems. For instance, often times a renal transporter is referred to as being involved in excretion of an ion or solute if it is found in the basolateral membrane when in fact its function may simply be the uptake into the cell of the ion or solute. Once inside the cell the ion can be effluxed back into the blood or it can be effluxed across the apical membrane into the tubular lumen. Therefore, it is important to be aware that there are uptake transporters (removing substances from the blood) and efflux transporters (returning substance to the blood) present in the epithelial cell basolateral membrane. Similarly, a renal transporter is often referred to as a reabsorption transporter if it is expressed in the apical membrane, however, there are both uptake (reabsorption into the cell) and efflux (excretion into the tubular lumen) transporters in the apical membrane as in the basolateral membrane.
The majority of renal transporters are members of the solute carrier (SLC) family of transporters and the ATP binding cassette (ABC) family of transporters. The following Tables list the majority of the transporters found in the human nephron separated by domains beginning with the proximal tubule. Those transporters that are localized to the basolateral membranes and, therefore, are involved in the uptake of ions or solutes from the blood or for effluxing ions or solutes back to the blood are listed first. Those transporters that are localized to the apical membranes and, therefore, are involved in the reabsorption of ions or solutes from the lumen of the tubule or for effluxing ions or solutes to the lumen for urinary excretion are listed next. The SLC family transporters in each membrane are listed first for each membrane followed by the ABC family transporters.

Additional proteins important in renal functioning are not classically defined as transporters but are designated as channels such as the the aquaporins (AQP: discussed below), the transient receptor potential (TRP) cation channels, and other various ion channels that include the calcium, chloride, and potassium channels.

It is important to note that much of the literature on renal transport systems reflects research on, and characterization of, transporters in rodent systems and there are certain species specific differences in transporter expression. As an example, the organic cation transporters encoded by the SLC22A1 (OCT1) gene and the SLC22A2 (OCT2) gene are both expressed in the basolateral membranes of the mouse proximal tubule epithelial cell. However, only the SLC22A2 (OCT2) gene encoded transporter is expressed in the human proximal tubule epithelial cell basolateral membrane.

Within each of the next sections there is a brief description of the major function of each nephron segment and a Table that includes an identification and description of transporters/channels present in that segment. The Tables are divided into four sections, two for basolateral transporters/channels (uptake from and efflux to blood) and two for apical membrane transporters/channels (reabsorption from and efflux to the lumen). Although the intention is to be comprehensive in presentation, there is likely to be omissions in the Tables.

Renal Water Balance

The renal channels responsible for water balance are members of the aquaporin (AQP) family of channels. Water transport through aquaporin channels occurs passively meaning no electrochemical gradient or energy (e.g. ATP) is required. The aquaporins are distributed throughout the nephron with some being expressed in both basolateral and apical membranes while others are expressed on intracellular membranes. Within the proximal tubule the AQP1, AQP7, AQP8, and AQP11 genes are expressed. The AQP1 protein is expressed on both the basolateral and apical membranes where its locations allow it to reabsorb and efflux water. Within the proximal tubule AQP1 is the primary aquaporin responsible for constitutive water reabsorption. The AQP1 gene is also expressed in the thin descending limb of the loop of Henle. The AQP7 channel is localized to the apical membrane of proximal tubule epithelial cells.

Several aquaporins are expressed in the connecting tubule (CNT) and collecting ducts, both cortical and medullary. The AQP2, AQP3, AQP4, AQP5, AQP6, and AQP8 genes are expressed in the CNT and cortical collecting ducts. Within the CNT and cortical collecting ducts AQP2, present in principal cells, is the primary aquaporin responsible for vasopressin-mediated regulation of fluid balance within the kidneys. In the absence of hormonal stimulation the AQP2 protein is stored within vesicles inside the cell. In response to vasopressin stimulation these vesicles fuse with the apical membrane of the principal cell and mediate rapid water reabsorption resulting in urine concentration. Mutations in the AQP2 gene are associated with a form of nephrogenic diabetes insipidus. The AQP3 and AQP4 genes are also expressed in principal cells where their encoded proteins are

localized to the basolateral membrane where they efflux water back to the blood. The AQP3 protein can facilitate movement of both water and glycerol across the membrane and as such is referred to as an aquaglyceroporin. The AQP6 gene is expressed in type A intercalated cells where it is primarily localized to intracellular vesicles. Like the AQP6 protein, AQP8 is also localized to intracellular membranes. With respect to the aquaporins, only the most significant member in each nephron segment will be included in the following Tables.

Major Renal Na^+ and K^+ Transporter

The major basolateral membrane transporter involved in renal Na^+ and K^+ exchange is the primary renal Na+/K+-ATPase which is composed of the α_1-subunit encoded by the ATP1A1 gene and the β_1-subunit encoded by the ATP1B1 gene. The basolateral Na^+/K^+-ATPase takes up two K^+ ions from the blood in exchange for the efflux of three Na^+ ions to the blood. The renal Na^+/K^+-ATPase is expressed in the basolateral membranes of epithelial cells throughout the nephron and is described here only and not listed in the following Tables.

Overview of Renal Acid-Base Balance

The kidneys play a critical role in the regulation of overall acid-base balance that ensures the maintenance of blood pH at around 7.4. The kidney accomplishes this critical function through a combination of H^+, HCO_3^-, and NH_3/NH_4^+ excretion and reabsorption. The proximal tubule reabsorbs approximately 80% of HCO_3^- present in the glomerular filtrate. Within the proximal tubule epithelial cell apical membrane and basolateral membrane, H+ and HCO3– transporters and extracellular and intracellular carbonic anhydrases (CAIV and CAII, respectively) are involved in the prcesses of acid-base regulation within this segment of the nephron. Apical membrane localized NHE3 (Na^+/H^+-exchanger 3: encoded by the SLC9A3 gene) and V-ATPase (H^+-ATPase) efflux H^+ into the tubular lumen in order to titrate HCO_3^- present in the glomerular filtrate. At the basolateral membrane, NBC1 (Na^+-bicarbonate cotransporter 1: encoded by the SLC4A4 gene) effluxes HCO_3^-, made *de novo* intracellularly via CAII, to the blood. The proximal tubule also produces HCO_3^- *de novo* in the context of ammonia production from glutamine. The apical membrane NHE3 and V-ATPase efflux the NH_4^+ into the tubule lumen and basolateral NBC1 effluxes the endogenously generated HCO_3^- to the blood. In the thick ascending limb (TAL), the apical membrane NHE3 and V-ATPase participate in H^+ efflux and the basolateral AE2 (anion exchanger 2: encoded by the SLA4A2 gene) transporter effluxes HCO_3^- to the blood in exchange for Cl^- uptake.

The collecting duct is also critical in the overall process of renal acid-base balance where the various specialized cell types (principal, type A intercalated and type B intercalated) carry out net H^+ exchange between the tubular lumen and the blood through the activities of V-ATPase, H^+/K^+-ATPase and various Cl^-/HCO_3^- exchangers. The renal H^+/K^+-ATPases are of two types determined by different α-subunits termed the gastric (often designated $HK_{\alpha 1}$) and colonic

(often designated $HK_{\alpha 2}$) isoforms encoded by the ATP4A and ATP12A genes, respectively. The H^+/K^+-ATPases also contain a β-subunit encoded by the ATP4B gene. Within the collecting duct apical membrane localized V-ATPase, H^+/K^+-ATPase, and Cl^-/HCO_3^- exchangers mediate the process of net H^+ efflux to the tubular lumen. Collecting duct epithelial cell basolateral membrane Cl^--HCO_3^- exchangers mediate net HCO_3^- efflux to the blood. In type A intercalated cells of the collecting duct apical membrane V-ATPase mediates H^+ efflux to the tubular lumen. In type B intercalated cells the V-ATPase is localized to the basolateral membrane and effluxes H^+ to the blood. The transport of H^+ from type A and type B intercalated cells is coordinated to the activity of various Cl^-/HCO_3^- exchangers on the opposite membrane. In type A intercalated cells the basolateral membrane localized Cl^-/HCO_3^- exchanger is AE1 (encoded by the SLC4A1 gene) and this transporter mediates HCO_3^- reabsorption from the blood. In type B intercalated cells the apical membrane localized Cl^-/HCO_3^- exchanger is called pendrin (encoded by the SLC26A4 gene) and this transporter mediates HCO_3^- efflux to the tubular lumen. Both intercalated cell types also express the renal H^+/K^+-ATPase in the apical membrane for H^+ efflux from the collecting duct to the tubular luman.

Ammonia and the resulting ammonium ion (NH_4^+), like H^+ and HCO_3^-, are central to renal acid-base balance. As discussed below, the proximal tubule is the location for endogenous ammonia production from the amino acid glutamine (termed ammoniagenesis). Approximately 50% of the newly generated ammonia produced in the proximal tubule is effluxed to the tubular lumen via the Na^+/H^+-exchanger 3 (NHE3; encoded by the SLC9A3 gene). The distal tubule and the collecting duct are major sites for NH_4^+ secretion which occurs via simultaneous efflux of H^+ and NH_3. The major transporters involved in this process are the Rhesus associated glycoproteins, RHBG and RHCG encoded by the RHBG (also identified as SLC42A2) and RHCG (also identified as SLC42A3) genes, respectively. The RHBG transporter is localized to the basolateral membrane of type A intercalated cells, whereas the RHCG transporter is localized to both the apical and the basolateral membranes of type A intercalated cells. Although at much lower levels RHBG and RHCG are also found in principal cells.

Renal Urea Transport and Urine Concentration

Urea represents the major nitrogen containing waste product of human metabolism. Indeed, approximately 80% of the nitrogen in the urine on a daily basis is in the form of urea. In addition to excretion of waste nitrogen, urea excretion is coupled to the regulation of the urine concentrating properties of the nephron, specifically within the collecting duct portion of the nephron (specifically the inner medullary collecting duct, IMCD).

Humans express two urea transporter genes, SLC14A1 and SLC14A2, that encode transporters identified as UT-B and UT-A, respectively. The SLC14A1

gene is located on chromosome 18q12.3 and is composed of 13 exons that generate six alternatively spliced mRNAs. There are two UT-B transporters are identified as UT-B1 and UT-B2 and their primary function is in the transport of urea in erythrocytes. The UT-B proteins are the basis of the Kidd blood group antigens. The expression of the UT-B1 isoform is ubiquitous being found in numerous human tissues in addition to erythrocytes. Within the kidney the UT-B1 isoform is found in the endothelial cells of the vessels (vasa recta) that are external to the collecting duct clusters. The UT-B2 isoform is only expressed in erythrocytes and the brain in humans.

The SLC14A2 gene encodes the renal urea transporters. The SLC14A2 gene is located close to the SLC14A1 gene on chromosome 18 and is composed of 23 exons. The SLC14A2 gene contains two distinct promoter elements, one that is in the typical position upstream of exon 1 and the other which resides within exon 12. The upstream promoter is termed the UT-Aα promoter and the internal promoter is termed the UT-Aβ promoter. As a result of the use of these two promoters and the consequences of alternative splicing at least four different UT-A transporter isoforms are generated in humans (six total are generated when considering all mammals) in distinct locations within the nephron and the rest of the body. The human UT-A isoforms that are identified as UT-A1, UT-A3, and UT-A6 are encoded by the mRNAs transcribed from the UT-Aα promoter of the human SLC14A2 gene while the UT-A2 isoform is encoded by the mRNA transcribed from the human UT-Aβ promoter. The UT-A3 protein is the N-terminal half of the UT-A1 protein while the UT-A2 protein is the C-terminal half of the UT-A1 protein. The UT-A6 protein is also common to the N-terminal region of the UT-A1 protein but is much shorter than the UT-A3 protein and the UT-A6 protein also contains unique sequences at it C-terminus.

The UT-A1 transporter is expressed in the apical membranes of epithelial cells of the inner medullary collecting duct (IMCD). The UT-A3 transporter is expressed in the basolateral membranes of the IMCD epithelial cells. However, the UT-A3 protein can be found in the apical membrane following vasopressin stimulation. The UT-A2 transporter is expressed in the basolateral membranes of epithelial cells of the thin descending limb of the loop of Henle. The UT-A1 and UT-A3 transporters are critical for urea reabsorption during antidiuresis in order to maintain the hypertonic state of the medullary interstitium (anatomically the spaces between the tubule cells and the endothelial cells of the blood vessels). In addition to renal localization the UT-A1 isoform is expressed in the human ear (cochlea), the UT-A2 isoform is expressed in the human heart and liver, the UT-A3 isoform is expressed in the human ear (cochlea), and the UT-A6 isoform is expressed in the human colon.

The amount of urea that enters the proximal tubule from the glomerular filtration apparatus is nearly identical to the concentration in the plasma. Under normal renal physiological conditions, 30%-50% of the filtered urea is excreted. Within the proximal tubule the concentration of urea increases such that by the time the glomerular filtrate reaches to descending limb of Henle the urea concentration is

50% higher than it was in the blood. This increase in concentration results from the reabsorption of water in the proximal tubule, secondary to salt reabsorption. Urea transport in the proximal tubule is not regulated by vasopressin but it is increased as the level of Na+ and Cl– transport is increased. The loop of Henle is permeable to urea due the presence of the UT-A2 transporter in the thin descending limb such that when the glomerular filtrate reaches the distal convoluted tubule (DCT) the concentration of urea can be on the order of 7 times that of the plasma. This level of urea concentrating occurs only under antidiuretic conditions. During water diuresis there is no proximal tubular urea transport and there is net urea reabsorption in the loop of Henle. Within the DCT there is little urea transport such that in general the concentration decreases to approximately 70% of the load in the glomerular filtrate. Within the collecting ducts, specifically the inner medullary collecting ducts (IMCD) the actions of the UT-A1 and UT-A3 transporters results in significant urea reabsorption. The tubular urine leaving the IMCD contains approximately 50% of the filtered load of urea.

One of the principal functions of the medullary collecting ducts is urine concentration. Urea and the urea transporters in the IMCD play critical roles in the processes of urine concentration indicating that urea does not serve the sole purpose of waste nitrogen disposal. Indeed, in individuals with protein deprivation there is a significant impairment in urine concentrating and this can be restored by urea infusion (in experimental animals) or by restoration of protein intake in humans. Urea has an effective osmolarity of 0 (zero) as does water, thus, it is highly effective at being used to regulate the osmolarity of the interstitium of the nephron. Vasopressin, which is released in response to hypothalamic osmoreceptors sensing the amount of water and Na^+ in the blood, functions in the role of urea transport and urine concentration. Within the IMCD the binding of vasopressin to the V_2 receptor (which is coupled to a G_s-type G-protein) triggers activation of PKA which phosphorylates the UT-A1 protein stimulating its mobilization to the apical membrane, thereby, increasing urea reabsorption as a means to maintain osmolarity under conditions of reduced water.

Proximal Tubule Transport Processes

The proximal tubule is where the vast majority of the ions and solutes in the glomerular filtrate are reabsorbed for transport back into the blood. One of the most important ions reabsorbed from the glomerular filtrate via the proximal tubule is Na^+ which is primarily, although certainly not exclusively, by the ubiquitously distributed Na^+,K^+-ATPase described above. The proximal tubule is also a major site for the regulation of the acid-base balance of the glomerular filtrate. This latter function is effected by the efflux of H^+ from the proximal tubule epithelial cells into the blood in exchange for bicarbonate ion in the glomerular filtrate.

With respect to proximal tubule function, in a general sense, roughly 70% of all the the ions and water in the glomerular filtrate are reabsorbed. Proximal tubular reabsorption rates are different for the various constituents in the glomerular filtrate. For example, 100% of the organic ions, particularly glucose, are reabsorbed, approximately 60%-70% of the calcium is reabsorbed, approximately 85% of phosphate ion is reabsorbed, approximately 65% of potassium ion is reabsorbed, and approximately 50% of the urea is reabsorbed. The proximal tubule is also the location where 99% of amino acids in the glomerular filtrate are reabsorbed. The majority of the calcium, magnesium, and phosphate that is reabsorbed by the proximal tubule is accomplished by passive paracellular transport with only 10%-15% occurring via active transport across the apical and basolateral membranes. Paracellular transport is that occurring between cells as opposed to transcellular transport which refers to transport through cells. Paracellular transport processes are regulated by tight junctions and by the electrochemical gradients established across the tubule via the actions of the numerous apical membrane-localized ion transporters.

Proximal Tubule Ammoniagenesis

Another important function of the proximal tubule is the generation of ammonia (NH_3) which is in equilibrium with ammonium ion (NH_4^+). The production of ammonia is referred to as ammoniagenesis. Although ammonia and ammonium ion excretion in the urine constitutes a portion of the total waste nitrogen excretion, ammoniagenesis in the kidney is critically important in acid-base regulation. The production, excretion, and reabsorption of bicarbonate (HCO_3^-), by the kidney, is a major contributor to the renal responsibility to regulate acid-base balance. However, on its own renal bicarbonate production is not sufficient, thus the need for ammonia generation. The ionization of NH_3 to NH_4^+ is an effective means to reduce the overall H^+ load, and thus, raise the pH of the blood during periods of acidosis.

The major source of nitrogen for proximal tubule ammoniagenesis is the amino acid glutamine which can yield two moles of NH_4^+ through the concerted actions of glutaminase and glutamate dehydrogenase, respectively. Proximal tubule glutamine reabsorption from the glomerular filtrate is accomplished via the action of the apical membrane associated Na^+-dependent neutral amino acid transporter 1 identified as B0AT1 and encoded by the SLC6A19 gene. Mutations in the SLC6A19 gene are the causes of Hartnup disorder. Glutamine is also taken up from the blood by proximal tubule cells via the basolateral membrane Na+-coupled neutral amino acid transporter 3 identified as SNAT3 which is encoded by the SLC38A3 gene. The biochemistry of ammonia release from glutamine is covered in detail in the Amino Acid Metabolism page.

In addition to releasing two moles of NH4+, the benefits of renal glutamine metabolism are that bicarbonate (HCO3–) is also generated. The HCO3– is derived from the TCA cycle-mediated oxidation of the 2-oxoglutarate that results from the glutaminase and glutamate dehydrogenase reactions. The HCO3– is then transported to the blood from the proximal tubule cells via the basolateral

membrane Na+-coupled bicarbonate transporter identified as NBC1 which is encoded by the SLC4A4 gene. Mutations in the SLC4A4 gene result in type 2 (proximal) renal tubular acidosis (type 2 RTA). The HCO3– produced by the proximal tubule via glutamine metabolism represents new HCO3– being added to the pool already in the blood, thereby enhancing the buffering capacity of the blood. Approximately 50% of the ammonia/ammonium produced from glutamine in the proximal tubule is effluxed to the tubular lumen via the Na^+/H^+-exchanger 3 (NHE3) which is encoded by the SLC9A3 gene. The remainder of the ammonia/ammonium enters the systemic circulation via the renal veins where it is picked up by the liver and incorporated into urea. Ammonia produced by the proximal tubule and effluxed to the lumen can be reabsorbed in the loop of Henle and finally excreted by the collecting duct.

Proximal Tubule Transporters/Channels

Gene	Common/Other Name	Functions / Comments
Basolateral Membrane Uptake from Blood		
SLC9A1	NHE1: Na^+/H^+ exchanger 1	uptake of Na^+ with simultaneous efflux of H^+
SLC9A4	NHE4: Na^+/H^+ exchanger 4	uptake of Na^+ with simultaneous efflux of H^+
SLC13A1	NaS1: Na^+/sulfate cotransporter	Na^+ and sulfate uptake; major contributor to renal sulfate homeostasis
SLC13A3	NaDC3: Na^+-dependent carboxylate cotransporter 3	Na^+ and carboxylate uptake; citrate, succinate, 2-oxoglutarate (α-ketoglutarate) uptake
SLC22A2	OCT2: organic cation transporter 2	excretion; organic cation uptake from blood; predominant organic cation transporter in the basolateral membranes of proximal tubule cells; major creatinine uptake transporter
SLC22A3	OCT3: organic cation transporter 3	excretion; organic cation uptake from blood; major creatinine uptake transporter

SLC22A6	OAT1: organic anion transporter 1	excretion; organic anion uptake from the blood in exchange for dicarboxylic acid such as glutarate or 2-oxoglutarate (α-ketoglutarate); involved in uric acid uptake from blood; functions with SLC22A8 (OAT3)
SLC22A7	OAT2: organic anion transporter 2	excretion; organic anion uptake from the blood in exchange for dicarboxylic acid such as glutarate or 2-oxoglutarate (α-ketoglutarate); uptake of uric acid; major creatinine uptake transporter; removes numerous drugs from blood (e.g. 5-flurouracil)
SLC22A8	OAT3: organic anion transporter 3	excretion; organic anion uptake from the blood in exchange for dicarboxylic acid such as glutarate or 2-oxoglutarate (α-ketoglutarate); involved in uric acid uptake from blood; functions with SLC22A8 (OAT1); removes numerous drugs from blood including methotrexate, indomethacin, and ciprofloxacin
SLC38A3	SNAT3: system N/A transporter 3	glutamine uptake from and efflux to blood
SLCO4C1	OATP4C1: organic anion transporting polypeptide 4C1	excretion; uptake from the blood; transports bile acids, peptides, certain drugs, conjugated steroids, thyroid hormones
Basolateral Membrane Efflux to Blood		
AQP1	aquaporin 1	major proximal tubule water reabsorbing channel; present in both basolateral and apical membranes for water reabsorption and efflux to the blood
SLC2A9	GLUT9; URATv1	SLC2A9 gene yields two alternatively spliced mRNAs generating variants identified as GLUT9a and GLUT9b; the two forms are asymmetrically distributed such that GLUT9a is found in the basolateral membrane while GLUT9b is found in the apical membrane; GLUT9a involved in uric acid, fructose, and glucose efflux back to blood
SLC3A2	4F2hc	constitutes the heavy chain of heteromeric amino acid transporters; associates with the light chain

		proteins encoded by the SLC7A5, SLC7A6, SLC7A7, SLC7A8, SLC7A10 and SLC7A11 genes; amino acid efflux to blood
SLC4A4	NBC1: Na^+-bicarbonate cotransporter 1	Na+ and bicarbonate efflux to blood; mutations in SLC4A4 gene associated with type 2 (proximal) renal tubular acidosis, RTA
SLC7A7	y^+LAT1: y^+L-type amino acid transporter 1	constitutes the light chain of a heteromeric cationic amino acid transporter; associates with the heavy chain protein encoded by the SLC3A2 gene (protein also identified as 4F2hc); cationic amino acid efflux to blood
SLC7A8	LAT2: L-type amino acid transporter 2	constitutes the light chain of a heteromeric cationic amino acid transporter; associates with the heavy chain protein encoded by the SLC3A2 gene (protein also identified as 4F2hc); cationic amino acid efflux to blood
SLC9A1	NHE1: Na^+/H^+ exchanger 1	efflux of H^+ with simultaneous uptake of Na^+
SLC9A4	NHE4: Na^+/H^+ exchanger 4	efflux of H^+ with simultaneous uptake of Na^+
SLC16A10	TAT1: T-type amino acid transporter 1	Na^+-independent aromatic amino acid (phenylalanine, tyrosine, and tryptophan) efflux to blood
SLC26A1	SAT1: sulfate anion transporter 1	sulfate efflux to blood; mutations in gene associated with hyperoxaluria and formation of calcium oxalate kidney stones
SLC38A3	SNAT3: system N/A transporter 3	glutamine uptake from and efflux to blood
SLC51A	OSTα: organic solute transporter alpha	reabsorption; functions as heterodimer with SLC51B (OSTβ); uptake of bile acids, steroids, and prostaglandin E2 (PGE2)
SLC51B	OSTβ: organic solute transporter	reabsorption; functions as a heterodimer with SLC51A (OSTα); uptake of bile acids, steroids, and prostaglandin E2 (PGE2)

	beta	
ABCA1		reabsorption; cholesterol and phospholipid transfer
ABCC1	MRP1: multidrug resistance associated protein 1	reabsorption; leukotriene C4 (LTC4); glutathione conjugated xenobiotics
ABCC3	MRP3: multidrug resistance associated protein 3	reabsorption; also called MOATD (multispecific organic anion transporter D) and CMOAT2 (canalicular multispecific organic anion transporter 2)
ABCC5	MRP5: multidrug resistance associated protein 5	reabsorption; uptake of cyclic nucleotides from tubular lumen; also called MOATC (multispecific organic anion transporter C)
ABCC6	MRP6: multidrug resistance associated protein 6	reabsorption; also called MOATE (multispecific organic anion transporter E)
Apical Membrane Uptake from Tubular Lumen		
AQP1	aquaporin 1	major proximal tubule water reabsorbing channel; present in both basolateral and apical membranes for water reabsorption from lumen and efflux to the blood
SLC1A1	EAAT3: excitatory amino acid transporter 3	high affinity glutamate transporter; also transports aspartate and cystine; Na^+ and H^+ taken up with amino acid with simultaneous K^+ efflux
SLC2A9	GLUT9; URATv1	SLC2A9 gene yields two alternatively spliced mRNAs generating variants identified as GLUT9a and GLUT9b; the two forms are asymmetrically distributed such that GLUT9a is found in the basolateral membrane while GLUT9b is found in the apical membrane; GLUT9b involved in uric acid, fructose, and glucose reabsorption from tubular lumen
SLC3A1	rBAT: renal basic amino acid	is a heavy chain subunit of heteromeric amino acid transporters; functions with the light chain subunit

	transporter	encoded by the SLC7A9 gene; cystine reabsorption along with amino acid efflux; mutations in gene cause type I cystinurias
SLC5A1	SGLT1: Na^+-glucose transporter 1	primarily expressed in the S2 segment; of little significance to renal glucose reabsorption
SLC5A2	SGLT2: Na^+-glucose transporter 2	predominantly expressed in the S1 segment; responsible for approximately 90% of glucose reabsorption
SLC5A8	SMCT1: sodium monocarboxylate transporter 1	uric acid reabsorption along with lactate efflux; functions with SLC5A12 (SMCT2); is a member of the sodium-glucose transporter family (SGLT)
SLC5A12	SMCT2: sodium monocarboxylate transporter 2	uric acid reabsorption along with lactate efflux; functions with SLC5A8 (SMCT1); is a member of the sodium-glucose transporter family (SGLT)
SLC6A15	B0AT2: B0 neutral amino acid transporter 2	reabsorption of proline, leucine, valine, isoleucine, and methionine along with Na^+
SLC6A18	B0AT3: B0 neutral amino acid transporter 3	neutral amino acid (glycine, alanine, methionine, serine, cysteine) reabsorption along with Na^+; apical membrane localization of SLC6A18 requires the protein called collectrin which is encoded by the TMEM27 gene
SLC6A19	B0AT1: B0 neutral amino acid transporter 1	neutral amino acid reabsorption along with Na^+; mutations in gene cause Hartnup disorder; apical membrane localization of SLC6A19 requires the protein called collectrin which is encoded by the TMEM27 gene
SLC6A20		uptake of proline, hydroxyproline, glycine, and betaine (trimethylglycine) along with Na^+; apical membrane localization of SLC6A20 requires the protein called collectrin which is encoded by the TMEM27 gene
SLC7A9	$b^{0,+}AT$	is a light chain subunit of heteromeric amino acid transporters; functions with the heavy chain

		subunit encoded by the SLC3A1 gene; cystine reabsorption along with amino acid efflux; mutations in gene cause non-type I cystinurias
SLC9A3	NHE3: Na^+/H^+ exchanger 3	major transporter involved in proximal tubule reabsorption of Na+ and HCO3– with simultaneous efflux of H+ or NH4+
SLC9A8	NHE8: Na^+/H^+ exchanger 8	uptake of Na+ with simultaneous efflux of H+; expressed at highest levels in the neonate
SLC10A2	ASBT: apical sodium bile transporter	reabsorption; H^+-coupled uptake of small peptides and β-lactam (e.g. penicillins and cephalosporins) antibiotics
SLC13A2	NaDC1: Na^+-dependent carboxylate cotransporter 1	Na^+ and carboxylate uptake; citrate, succinate, 2-oxoglutarate (α-ketoglutarate) uptake; major regulator of renal dicarboxylate reabsorption
SLC15A1	PEPT1: peptide transporter 1	reabsorption; H^+-coupled uptake of small peptides and β-lactam (e.g. penicillins and cephalosporins) antibiotics, angiotensin coverting enzyme (ACE) inhibitors, several prodrugs
SLC15A2	PEPT2: peptide transporter 2	reabsorption; H^+-coupled uptake of small peptides and β-lactam (e.g. penicillins and cephalosporins) antibiotics, angiotensin coverting enzyme (ACE) inhibitors, several prodrugs
SLC20A2	Pit-2: inorganic phosphate (P_i) transporter 2	member of the type III Na^{-+}-phosphate cotransporter family; phosphate ion (as $H_2PO_4^-$) uptake simultaneously with Na^+; considered to play a minor role in phosphate reabsorption
SLC22A4	OCTN1: multispecific organic cation transporter 1	organic cation efflux in exchange for H^+ uptake from lumen; reabsorption of carnitine, ergothioneine (thiourea derivative of histidine made by bacteria), and acetylcholine
SLC22A5	OCTN2: multispecific organic cation	Na^+-dependent carnitine and organic cation reabsorption

	transporter 2	
SLC22A7	OAT2: organic anion transporter 2	organic anion uptake from the lumen in exchange for dicarboxylic acid such as glutarate or 2-oxoglutarate (α-ketoglutarate); involved in creatinine reabsorption
SLC22A10	OAT5: organic anion transporter 5	organic anion uptake from the lumen in exchange for dicarboxylic acid such as glutarate or 2-oxoglutarate (α-ketoglutarate)
SLC22A11	OAT4: organic anion transporter 4	reabsorption of uric acid in exchange for carboxylate (primarily 2-oxoglutarate) efflux; also involved in transport of diuretics into the tubular lumen for excretion
SLC22A12	URAT1: urate transporter 1	reabsorption; major transporter involved in uric acid reabsorption; functions in exchange for carboxylate with primary exchange being lactate; target of uricosuric drugs (e.g. probenecid, benzobromarone); inhibition can lead to lactate retention and lactic acidosis
SLC22A13	OAT10: organic anion transporter 10	reabsorption of uric acid in exchange for monocarboxylate efflux; also involved in uptake of nicotinate
SLC23A1	SVCT1: Na^+-dependent vitamin C transporter 1	reabsorption of ascorbate
SLC26A1	SAT1: sulfate anion transporter 1	sulfate and oxalate reabsorption; mutations in gene associated with hyperoxaluria and formation of calcium oxalate kidney stones
SLC26A6		reabsorption of Cl^- in exchange for HCO_3^- efflux; also involved in oxalate and sulfate anion transport
SLC28A1	CNT1: Na^+-dependent concentrative nucleoside transporter 1	reabsorption; uptake of nucleosides

SLC28A2	CNT2: Na^+-dependent concentrative nucleoside transporter 2	reabsorption; uptake of nucleosides
SLC28A3	CNT3: Na^+-dependent concentrative nucleoside transporter 3	reabsorption; uptake of nucleosides
SLC29A1	ENT1: equilibrative nucleoside transporter 1	reabsorption; uptake of nucleosides
SLC29A2	ENT2: equilibrative nucleoside transporter 2	reabsorption; uptake of nucleosides
SLC34A1	NPT2a (NPT2): Na^+-phosphate co-transporter 2a	primary transporter for uptake of phosphate ion (as HPO_4^{2-}) along with Na^+; transports three Na^+ with each phosphate ion; functions in concert with NPT2c for phosphate reabsorption
SLC34A3	NPT2c: Na^+-phosphate co-transporter 2c	primary transporter for uptake of phosphate ion (as HPO_4^{2-}) along with Na^+; transports two Na^+ with each phosphate ion; functions in concert with NPT2a for phosphate reabsorption
SLC36A1	PAT1: proton amino acid transporter 1	H^+-coupled proline, glycine, and alanine uptake
SLC36A2	PAT2: proton amino acid transporter 2	H^+-coupled proline, glycine, and alanine uptake
SLCO1A2	OATP1A2/OATPA: organic anion transporting	OATP1A2 is human homolog of rodent OAT-K1/K2; formerly identified as SLC21A3; Na+-independent uptake of bile acids

	polypeptide A	
SLCO1B1	OATP1B1/OATPC: organic anion transporting polypeptide C	OATP1B1 is human homolog of rodent OATP1A4; formerly identified as SLC21A6; Na+-independent uptake of bilirubin, glucuronidated estradiol, leukotriene C4 (LTC4)
SLCO2A1	OATP2A1	OATP1B1 is human homolog of rodent OATP1A6; formerly identified as SLC21A2; Na+-independent uptake of prostaglandins
SLCO2B1	OATP2B1/OATPB: organic anion transporting polypeptide B	formerly identified as SLC21A9; Na+-independent uptake of sulfated steroids
SLCO3A1	OATP3A1/OATPD: organic anion transporting polypeptide D	formerly identified as SLC21A11; Na+-independent uptake of prostaglandins, thyroxine (T4), and vasopressin
SLCO4A1	OATP4A1/OATPE: organic anion transporting polypeptide E	OATP4A1 is human homolog of rodent OATP1A1; formerly identified as SLC21A12; Na+-independent uptake of thyroid hormones and bile acids
TRPC1		transient receptor potential canonical 1; Ca2+ reabsorption transporter
Apical Membrane Efflux to Tubular Lumen		
SLC9A3	NHE3: Na^+/H^+ exchanger 3	major transporter involved in proximal tubule reabsorption of Na+ and HCO3– with simultaneous efflux of H+
SLC9A8	NHE8: Na^+/H^+ exchanger 8	uptake of Na+ with simultaneous efflux of H+; expressed at highest levels in the neonate
SLC17A1	NPT1: Na^+-phosphate transporter 1	uric acid efflux; phosphate reuptake via Na+ co-transport; missense mutation converting Ile at position 269 to Thr (I269T mutation) enhances urate excretion preventing renal under excretion gout
SLC17A3	NPT4: Na^+-phosphate	uric acid efflux; loop diuretics, such as furosemide and bumetanide interact with SLC17A3 and are excreted; competition for excretion may be

	transporter 4	involved in diruetic-induced hyperuricemia
SLC22A4	OCTN1: multispecific organic cation transporter 1	organic cation efflux in exchange for H^+ uptake from lumen; also functions in reabsorption (as described above) of carnitine; involved in renal efflux of gabapentin and mutations in SLC22A4 gene associated reduced secretion of the drug
SLC26A6		efflux of HCO_3^- in exchange for Cl^- reabsorption; also involved in oxalate and sulfate anion transport
SLC47A1	MATE1: multidrug and toxin extrusion protein 1	creatinine and organic cation efflux to tubular lumen; in addition to organic cations SLC47A1 also transports the anionic steroid estrone sulfate; also transports several drugs such as metformin, cisplatin, cimetidine, topotecan, procainamide, acyclovir, and ganciclovir
SLC47A2	MATE2-K: multidrug and toxin extrusion protein 2	creatinine and organic cation efflux to tubular lumen; effluxes several drugs similar to those transported by SLC47A1 such as metformin, cimetidine, and procainamide; the antibiotic pyrimethamine is a potent inhibitor of SCL47A2 function
ABCB1	MDR1: multidrug resistance protein 1	excretion; also called P-gp or PGY1 (P-glycoprotein 1)
ABCC2	MRP2: multidrug resistance associated protein 2	excretion; efflux of non-bile organic ions; also called CMOAT (canalicular multispecific organic anion transporter)
ABCC4	MRP4: multidrug resistance associated protein 4	excretion; efflux of uric acid; also called MOATB (multispecific organic anion transporter B)
ABCG2	BCRP: breast cancer resistance protein	excretion; involved in uric acid efflux; efflux of xenobiotics

Loop of Henle

The loop of Henle gets its name from the German anatomist who first described this anatomical structure of the nephron, Friedrich Gustav Jakob Henle. The loop of Henle is composed of descending and ascending limbs which both can be divided into two broad domains termed thin and thick. The upper part of the descending limb is sometimes referred to as the thick descending limb although most often the entirety of the descending limb is described as only being thin. The ascending limb is clearly divided anatomically and functionally into thin and thick segments with the most significant transport processes occurring with the thick ascending limb (TAL). The primary function of the loop of Henle is water, sodium, and chloride (salt) reabsorption from the glomerular filtrate. This reabsorption process in the loop of Henle results in the formation of a concentration gradient within the medullary portion of the loop. The descending limb of the loop is highly permeable to water but relatively impermeable to ions and solutes. Conversely the ascending limb of the loop is permeable to ions while being relatively impermeable to water. This difference in water and ion permeability between the descending and ascending limbs of the loop of Henle is what results in the concentration gradient to the glomerular filtrate.

Thick Ascending Limb, TAL

The thick ascending limb (TAL) of the loop of Henle is principally responsible for sodium and chloride ion reabsorption from the glomerular filtrate. Approximately 25%-30% of these ions are reabsorbed by the transporters of the epithelial cells in the TAL. The major transporter tasked with sodium and chloride reabsorption is the SLC12A1 gene encoded protein expressed in the apical membrane of the cell. The SLC12A1 encoded protein is more commonly called NKCC2 ($Na^+/K^+/2$ Cl^- cotransporter 2). While reabsorbing salt the TAL reabsorbs no water which results in a dilution of the ionic content of the lumenal fluid. Absorption of sodium and chloride, via the action of NKCC2, requires that an electrochemical gradient be established. This gradient is generated via the action of the ubiquitously expressed Na^+,K^+-ATPases expressed in the basolateral membranes of the epithelial cells throughout the nephron as discussed earlier. The Na^+ reabsorbed by NKCC2 is effluxed to the blood across the basolateral membrane by the Na^+/K^+-ATPase while the Cl^- is effluxed to the blood via the basolateral K^+/Cl^- cotransporter encoded by the SLC12A7 gene. The SLC12A7 encoded protein is commonly called KCC4 (K^+/Cl^- cotransporter 4). The NKCC2 reabsorbed Cl^- can also be effluxed to the blood via the basolateral voltage-gated Cl^- transporter encoded by the CLCNKB gene. The CLCNKB encoded protein is commonly called ClC-Kb (the mouse protein is ClC-Kb2). Some of the reabsorbed K^+ is effluxed back into the lumen through the action of the KCNJ1 encoded potassium channel more commonly called ROMK (renal outer medullary potassium channel).

Within the loop of Henle approximately 20% of the Ca^{2+} in the glomerular filtrate is reabsorbed, all of which occurs in the TAL. Calcium reabsorption in the TAL occurs by both active transport across the cell membrane (transcellular) and by paracellular passive transport with the bulk occurring via the paracellular route. The paracellular transport of Ca^{2+} in the TAL is driven by the electrochemical gradient that is established across the tubule via the actions of the apical transporters ROMK and NKCC2.

Thick Ascending Limb (TAL) Transporters/Channels

Gene	Common/Other Name	Functions / Comments
Basolateral Membrane Uptake from Blood		
SLC9A4	NHE4: Na^+/H^+ exchanger 4	uptake of Na^+ with simultaneous efflux of H^+; expressed throughout nephron but highest in TAL
TRPV4	transient receptor potential, vanilloid 4	calcium uptake from blood
Basolateral Membrane Efflux to Blood		
SLC9A4	NHE4: Na^+/H^+ exchanger 4	efflux of H^+ and NH_4^+ with simultaneous uptake of Na^+; expressed throughout nephron but highest in TAL
SLC12A7	KCC4: potassium-chloride cotransporter 4	effluxes both K^+ and Cl^- to blood
CLCNKA	ClC-Ka: chloride channel Ka	voltage-gated chloride channel; exclusively expressed in the kidney and inner ear; requires an accessory β-subunit called barttin encoded by the BSND gene; minor chloride transporter of the TAL; effluxes Cl^- ion to the blood that was reabsorbed from the glomerular filtrate via the actions of SLC12A1 (NKCC2) and SLC12A3 (NCC)
CLCNKB	ClC-Kb: chloride channel Kb	voltage-gated chloride channel; exclusively expressed in the kidney and inner ear; requires an accessory β-subunit called barttin encoded by the

		BSND gene; predominant chloride transporter of the TAL; effluxes Cl– ion to the blood that was reabsorbed from the glomerular filtrate via the actions of SLC12A1 (NKCC2) and SLC12A3 (NCC); mutations in gene are the cause of Bartter syndrome type 3
KCNJ10	$K_{ir}4.1$	member of the inwardly-rectifying potassium channel family; coupled to the actions of the Na+/K+-ATPase for efflux of K+ to the blood
KCNJ16	$K_{ir}5.1$	member of the inwardly-rectifying potassium channel family; coupled to the actions of the Na+/K+-ATPase for efflux of K+ to the blood
Apical Membrane Uptake from Tubular Lumen		
SLC9A2	NHE2: Na^+/H^+ exchanger 2	uptake of Na^+ with simultaneous efflux of H^+
SLC9A3	NHE3: Na^+/H^+ exchanger 3	uptake of Na^+ with simultaneous efflux of H^+
SLC12A1	NKCC2: $Na^+/K^+/2$ Cl^- cotransporter 2	transports one Na+, one K+, and two Cl– ions; exclusively expressed in the TAL; responsible for all of the NaCl reabsorption occurring in the TAL; also responsible for NH4+ reabsorption; at least six isoforms result from alternative splicing and these different forms are differentially distributed along the TAL and also exhibit differences in ion transport properties; trafficking of NKCC2 in thick ascending limb cells is controlled by its state of phosphorylation; phosphorylation of NKCC2 is carried out by WNK kinases following their activation by vasopressin; NKCC2 is the target of the loop diuretics furosemide and bumetanide; mutations in gene are the cause of Bartter syndrome type 1
SLC26A6		reabsorption of Cl– in exchange for HCO3– efflux; also involved in oxalate and sulfate anion transport
TRPP2		transient receptor potential polycystin 2; Ca^{2+} reabsorption transporter
TRPV4		transient receptor potential vanilloid 4; Ca^{2+} resoprtion transporter

Apical Membrane Efflux to Tubular Lumen		
SLC9A2	NHE2: sodium hydrogen (H^+) exchanger 2	efflux of H^+ with simultaneous uptake of Na^+
SLC26A6		efflux of HCO_3^- in exchange for Cl^- reabsorption; also involved in oxalate and sulfate anion transport
KCNJ1	ROMK: renal outer medullary potassium channel	K^+ efflux to lumen; members of the KCNJ family of inwardly rectifying voltage-gated potassium channels are also identified a Kir channels with ROMK being Kir1.1 (three isoforms due to alternative splicing: Kir1.1a, Kir1.1b, and Kir1.1c); aldosterone activates ROMK by inducing its phosphorylation by SGK1 (serum/glucocorticoid regulated kinase 1) which results in potassium secretion; mutations in gene are the cause of Bartter syndrome type 2

Distal Convoluted Tubule, DCT

The distal convoluted tubule (DCT) is a short segment of the nephron that represents the region between the macula densa and collecting duct. The primary function of the DCT is the regulation of extracellular fluid volume and electrolyte homeostasis. While carrying out ion transport, the epithelial cells of the DCT remain relatively impermeable to water. Cells of the DCT are responsive to the actions of the hormones angiotensin II and aldosterone with the late convoluted tubule region (denoted DCT2) representing a portion of the aldosterone-sensitive distal nephron which includes the connecting tubule (CNT) and the collecting duct. The basolateral membranes of the epithelial cells of the DCT have the highest concentrations of the Na+/K+-ATPase of all cells along the nephron. The DCT epithelial cells reabsorb Na+ and Cl– ions across the apical membrane, primarily via the actions of the thiazide-sensitive sodium and chloride cotransporter identified as NCC (encoded by the SLC12A3 gene). Thiazides represent a class of diuretic drugs used in the treatment of hypertension and edema. The epithelial cells of the DCT are also important for magnesium reabsorption. Mutations in genes encoding transporters and channels found in the DCT are associated with several diseases in humans including Bartter syndrome, Gitelman syndrome, familial hyperkalemic hypertension, EAST syndrome (Epilepsy, Ataxia, Sensorineural deafness, and salt-wasting renal Tubulopathy), and hereditary hypomagnesemias.

The DCT contributes to overall Ca^{2+} reabsorption accounting for approximately 10%-15% of the total reabsorption. However, unlike in the proximal tubule and the TAL of the loop pof Henle, all of the Ca^{2+} reabsorption in the DCT occurs via active (transcellular) transport. The active transport of Ca2+, within the DCT, is regulated by parathyroid hormone, PTH. The apical membrane associated transient receptor potential vanilloid 5 (TRPV5) transporter is the major Ca2+ uptake transporter in the DCT. The intracellular Ca2+ is then transported across the cell to the basolateral membrane via the calcium-binding protein, calbindin-D28K. Efflux of the reabsorbed Ca2+ to the blood occurs through the actions of the basolateral membrane transporters encoded by the SCL8A1 and ATP2B1 genes. The transporter encoded by the SLC8A1 gene is identified as NCX1 (Na^+/Ca^{2+} exchanger 1). The transporter encoded by the ATP2B1 gene is identified as PMCA1b (plasma membrane Ca^{2+} transporter 1b).

Distal Convoluted Tubule Transporters/Channels

Gene	Common/Other Name	Functions / Comments
Basolateral Membrane Uptake from Blood		
SLC8A1	NCX1: Na^+/Ca^{2+}-exchanger 1	primarily localized to the late DCT (DCT2); uptake of Na^+ in exchange for efflux of Ca^{2+} to blood
SLC12A2	NKCC1: $Na^+/K^+/2$ Cl^- cotransporter 1	primarily localized to the late DCT (DCT2); uptake of ammonia (NH_3) from the blood along with Na^+, K^+, and Cl^-
TRPV5		transient receptor potential vanilloid 5; Ca^{2+} uptake channel; present in the late DCT2 region; can form heteromeric complexes with TRPV6; co-localizes with the calcium-binding protein calbindin-D_{28K}
Basolateral Membrane Efflux to Blood		
ATP2B1	PMCA1b: plasma membrane Ca^{2+} transporter 1b	ATP-hydrolysis-mediated Ca^{2+} efflux; expressed in the late DCT region (DCT2); the PMCA1b protein isoform is derived from a specific alternatively spliced mRNA from the ATP2B1 gene
SLC8A1	NCX1: Na^+/Ca^{2+}-	primarily localized to the late DCT (DCT2) and

	exchanger 1	connecting tubule (CNT); effluxes Ca^{2+} to blood in exchange for uptake of Na^{+}
SLC12A7	KCC4: potassium-chloride cotransporter 4	effluxes both K^{+} and Cl^{-} to blood
CLCNKB	ClC-Kb: chloride channel Kb	voltage-gated chloride channel; exclusively expressed in the kidney and inner ear; requires an accessory β-subunit called barttin encoded by the BSND gene; predominant chloride transporter of the TAL; effluxes Cl– ion to the blood that was reabsorbed from the glomerular filtrate via the actions of SLC12A1 (NKCC2) and SLC12A3 (NCC); mutations in gene are the cause of Bartter syndrome type 3
CNNM2	cyclin and CBS domain divalent metal cation transport mediator 2	involved in Mg2+ efflux to blood
KCNJ10	$K_{ir}4.1$	member of the inwardly-rectifying potassium channel family; coupled to the actions of the Na+,K+-ATPase for efflux of K+ to the blood
KCNJ16	$K_{ir}5.1$	member of the inwardly-rectifying potassium channel family; coupled to the actions of the Na+,K+-ATPase for efflux of K+ to the blood
Apical Membrane Uptake from Tubular Lumen		
SLC9A2	NHE2: sodium hydrogen (H^{+}) exchanger 2	uptake of Na^{+} with simultaneous efflux of H^{+}
SLC12A3	NCC: Na^{+}/Cl^{-} cotransporter	major aldosterone-sensitive transporter in the DCT; also responsive to angiotensin II, insulin, and vasopressin; intracellular trafficking of NCC regulated by WNK kinase phosphorylation; transporter directly inhibited by thiazide diuretics; associated with epithelial sodium (Na+) channel, ENaC
SLC26A6		reabsorption of Cl– in exchange for HCO3– efflux; also involved in oxalate and sulfate anion transport

SCNN1A	ENaC α-subunit	forms a heterotrimeric Na+ channel with the SCNN1B and SCNN1G encoded proteins; the complex localizes with NCC protein in the DCT; mutations in gene result in pseudohypoaldosteronism type 1
SCNN1B	ENaC β-subunit	forms a heterotrimeric Na^+ channel with the SCNN1A and SCNN1G encoded proteins; the complex localizes with NCC protein in the DCT; mutations in gene result in pseudohypoaldosteronism type 1
SCNN1G	ENaC γ-subunit	forms a heterotrimeric Na^+ channel with the SCNN1A and SCNN1B encoded proteins; the complex localizes with NCC protein in the DCT
TRPM6		transient receptor potential melastatin 6; primarily involved in Mg^{2+} resoprtion but may transport Ca^{2+} as well; forms homotetramers and also heterotetramers with TRPM7
TRPP2		transient receptor potential polycystin 2; Ca^{2+} resoprtion transporter
TRPV4		transient receptor potential vanilloid 4; Ca^{2+} resoprtion transporter
TRPV5		transient receptor potential vanilloid 5; expressed in the late DCT region (DCT2); major Ca^{2+} reabsoprtion transporter; can form heteromeric complexes with TRPV6; co-localizes with the calcium-binding protein calbindin-D_{28K}
TRPV6		transient receptor potential vanilloid 6; Ca^{2+} resoprtion transporter
Apical Membrane Efflux to Tubular Lumen		
SLC9A2	NHE2: sodium hydrogen (H^+) exchanger 2	efflux of H^+ with simultaneous uptake of Na^+
SLC26A6		efflux of HCO_3^- in exchange for Cl^- reabsorption;

		also involved in oxalate and sulfate anion transport
KCNA1	$K_v1.1$	member of the voltage-gated potassium channel subfamily A; efflux of K^+ to the lumen

Connecting Tubule (CNT) and Collecting Duct

The connecting tubule (CNT) and the collecting duct represent the predominant aldosterone-sensitive region of the distal nephron. The function of aldosterone in this region of the nephron is to ensure that there is appropriate regulation of sodium (Na+) absorption from the glomerular filtrate in order to maintain whole body Na+ balance. The major transporter within the epithelial cells of the CNT and the collecting duct that is responsible for this critical Na+ balance is identified as ENaC (epithelial Na+ channel). The level of expression of the ENaC channel is regulated by aldosterone. The ENaC channel is composed of three subunits (α, β, and γ) that are encoded by three distinct genes that are member of the large family of sodium ion channels. The three genes encoding proteins of the ENaC are SCNN1A (α-subunit), SCNN1B (β-subunit), and SCNN1G (γ-subunit). The transepithelial transport of Na+ within the CNT and collecting duct epithelial cells involves ENaC present in the apical membrane and the renal Na+,K+-ATPase that is distributed in the basolateral membranes of epithelial cells along the nephron. In addition to aldosterone-sensitive Na+ reabsorption, the CNT and the collecting duct are responsible for K+ excretion, contribute to acid (H+) secretion, and also participate in regulation of magnesium and calcium reabsorption.

As described earlier, the epithelial cells of the CNT and collecting ducts (as well as within the distal tubule) are of three distinct types. These cell types are the principal cells and the intercalated cells identified as type A (alpha) and type B (beta). Principal cells reabsorb Na+ and excrete K+. Principal cells are the major cell types that respond to the actions of aldosterone. Type A intercalated cells reabsorb both K^+ and HCO_3^- and they excrete H^+. Type B intercalated cells function in opposition to type A cells such that they secrete HCO_3^- and reabsorb H^+. The differences in function between type A and type B intercalated cells is due, in part, to the opposing distributions of various transporter proteins which, for example, places a particular transporter in the apical membrane of a type A cell and the same transporter in the basolateral membrane of a type B cell.

Regulation of potassium balance via cells of the CNT is primarily due to the function of the renal outer medullary potassium (K^+) channel identified as ROMK. The ROMK protein is encoded by the KCNJ1 gene. The ROMK channel is present in the apical membranes of principal cells. Water reabsorption is also a critical function of the CNT and collecting duct and is the function of the vasopressin-responsive aquaporin, AQP2. The AQP2 channel is located in the apical membrane of principal cells. Activity of AQP2 is controlled via the actions of the angiotensin 1 receptors (AT1R) following their activation by binding angiotensin II.

Reabsorption and excretion of H+ within the CNT and collecting duct occurs via the actions of the V-ATPase complex (also identified as the H+-ATPase) present in the apical membrane of type A intercalated cells and the basolateral membrane of type B intercalated cells. The V-ATPase is composed of multiple subunits amassed into two distinct domains. The V_1 complex is the cytosolic catalytic complex and is composed of eight different subunits encoded by eight distinct genes. The V_0 complex is the transmembrane portion of the V-ATPase complex and is composed of at least five subunits encoded by distinct genes.

As indicated above in the discussion of the distal convoluted tubule, active Ca^{2+} reabsorption is restricted to the late distal convoluted (DCT2) and to the connecting tubules (CNT). Within these regions of the distal nephron approximately 10–15% of the total Ca^{2+} is reabsorbed with the majority being transported by the apical membrane localized transient receptor potential vanilloid 5 (TRPV5). Following uptake of Ca2+ at the apical membrane, the calcium-binding protein identified as calbindin-D28K, whose synthesis is stimulated by the bioactive form of vitamin D (calcitiol), sequesters the ion and transports it to the basolateral membrane where it can be effluxed back to the blood. This Ca2+ efflux is carried out by either the NCX1 (Na+-Ca2+ exchanger 1: encoded by the SLC8A1 gene) or the PCMA1b (plasma membrane Ca2+ transporter 1b: encoded by the ATP2B1 gene) transporters.

In addition to the actions of vasopressin and aldosterone in the CNT and collecting duct to regulate water, Na+, and K+ balance, this region of the nephron also responds to numerous additional hormonal, chemical, and physical inputs. Some of these inputs include nitric oxide (NO), bradykinin, prostaglandin E2 (PGE2), and ATP.

Connecting Tubule and Collecting Duct Transporters/Channels

Gene	Common/Other Name	Primary Cell Type	Functions / Comments
Basolateral Membrane Uptake from Blood			
SLC4A1	AE1: anion exchanger 1	Type A	Cl^-/HCO_3^- exchanger; Cl^- absorption from blood in exchange for HCO_3^- efflux to blood; is an N-terminally truncated isoform of the erythrocyte-specific protein which is also identified as BND3 (erythrocyte band 3 protein)
SLC8A1	NCX1: Na^+/Ca^{2+}-exchanger 1		effluxes Ca^{2+} to blood in exchange for uptake of Na^+

SLC12A2	NKCC1: $Na^+/K^+/2Cl^{-+}$ cotransporter type 1	Type A	uptake of ammonia (NH_3) from the blood along with Na^+, K^+, and Cl^-
SLC26A7		Type A	HCO_3^- in exchange for uptake Cl^-; also involved in oxalate and sulfate anion transport
RHBG	Rh blood group antigen B	Type A	the RHBG gene is also identified as the SLC42A2 gene; ammonia (NH_3) uptake from blood
RHCG	Rh blood group antigen C	Type A	the RHCG gene is also identified as the SLC42A3 gene; ammonia (NH_3) uptake from blood; also present in the apical membrane for NH_3 excretion
Basolateral Membrane Efflux to Blood			
ATP2B1	PMCA1b: plasma membrane Ca^{2+} transporter 1b	Type A	ATP-hydrolysis-mediated Ca^{2+} efflux; the PMCA1b protein isoform is derived from a specific alternatively spliced mRNA from the ATP2B1 gene
SLC4A1	AE1: anion exchanger 1	Type A	Cl^-/HCO_3^- exchanger; is an N-terminally truncated isoform of the erythrocyte-specific protein which is also identified as BND3 (erythrocyte band 3 protein); Cl^- absorption from blood in exchange for HCO_3^- efflux to blood
SLC4A2	AE2: anion exchanger 2	Type A	Cl^-/HCO_3^- exchanger; Cl^- absorption from blood in exchange for HCO_3^- efflux to blood
SLC4A3	AE3: anion exchanger 3	Type A	Cl^-/HCO_3^- exchanger; Cl^- absorption from blood in exchange for HCO_3^- efflux to blood
SLC4A9	AE4: anion exchanger 4	Type A	Na^+ and HCO_3^- efflux to blood; expressed exclusively in the kidney

SLC8A1	NCX1: Na^+/Ca^{2+}-exchanger 1		effluxes Ca^{2+} to blood in exchange for uptake of Na^+
SLC12A7	KCC4: $K^+/2\ Cl^-$ cotransporter 4	Type B	K^+ and Cl^- efflux to blood
SLC26A7		Type A	Cl– efflux in exchange for HCO3– uptake; also involved in oxalate and sulfate anion transport
CLCNKB	ClC-Kb: chloride channel Kb	Type A	voltage-gated chloride channel; exclusively expressed in the kidney and inner ear; requires an accessory β-subunit called barttin encoded by the BSND gene; effluxes Cl– ion to the blood; mutations in gene are the cause of Bartter syndrome type 3
KCNJ10	$K_{ir}4.1$	Principal	member of the inwardly-rectifying potassium channel family; coupled to the actions of the Na+,K+-ATPase for efflux of K+ to the blood
KCNJ16	$K_{ir}5.1$	Principal	member of the inwardly-rectifying potassium channel family; coupled to the actions of the Na+,K+-ATPase for efflux of K+ to the blood
V-ATPase	H^+-ATPase	Type B	H+ efflux to blood occurs via V-ATPase present in type B intercalated cells; multisubunit complex composed of a cytoplasmic catalytic (V1) complex of eight proteins and a transmembrane (V0) complex composed of at least five subunits; all subunits of the V0 and V1 complexes are encoded by different genes
Apical Membrane Uptake from Tubular Lumen			
ATP4A	H^+/K^+-ATPase	Principal	α_1-subunit of H^+/K^+-ATPase (often designated $HK_{\alpha1}$); major transporter involved in K^+ reabsorption
ATP12A	H^+/K^+-ATPase	Principal	α_2-subunit of H^+/K^+-ATPase (often designated $HK_{\alpha2}$); major transporter involved in K^+ reabsorption
ATP4b	H^+/K^+-ATPase	Principal	β-subunit of H^+/K^+-ATPase; major

			transporter involved in K^+ reabsorption
AQP2	aquaporin 2	Principal	major vasopressin-responsive water channel in the CNT and collecting duct
SLC26A6		Type A	reabsorption of Cl^- in exchange for HCO_3^- efflux; also involved in oxalate and sulfate anion transport
SCNN1A	ENaC: epithelial sodium channel; α-subunit	Principal	forms a heterotrimeric non-voltage gated ameloride-sensitive Na^+ channel with the SCNN1B and SCNN1G encoded proteins; forms the primary Na^+ transporter in the connecting tubule and collecting ducts; loss-of-function mutations in gene result in pseudohypoaldosteronism type 1 (neonatal salt-wasting hyperkalemia); gain-of-function mutations in gene result in Liddle syndrome (characterized by hypertension and hypokalemia)
SCNN1B	ENaC: epithelial sodium channel; β-subunit	Principal	forms a heterotrimeric non-voltage gated ameloride-sensitive Na^+ channel with the SCNN1A and SCNN1G encoded proteins; forms the primary Na^+ transporter in the connecting tubule and collecting ducts; loss-of-function mutations in gene result in pseudohypoaldosteronism type 1 (neonatal salt-wasting hyperkalemia); gain-of-function mutations in gene result in Liddle syndrome (characterized by hypertension and hypokalemia)
SCNN1G	ENaC: epithelial sodium channel; γ-subunit	Principal	forms a heterotrimeric non-voltage gated ameloride-sensitive Na^+ channel with the SCNN1A and SCNN1B encoded proteins; forms the primary Na^+ transporter in the connecting tubule and collecting ducts;
SLC4A8	NDCBE: Na^+-driven Cl^-/HCO_3^-	Type B	Na^+ and HCO_3^- reabsorption coupled to Cl^-

	exchanger		efflux; protein is also identified as NBC3
SLC26A4	Pendrin	Type B	Cl^- uptake coupled to HCO_3^- efflux; originally identified as mutated gene in Pendred syndrome which is characterized by hypothyroidism, goiter, and sensorineural deafness
TRPC3			transient receptor potential canonical 3; collecting duct only; Ca^{2+} resoprtion transporter
TRPC6			transient receptor potential canonical 6; collecting duct only; Ca^{2+} resoprtion transporter
TRPV4			transient receptor potential vanilloid 4; Ca^{2+} resoprtion transporter
TRPV5			transient receptor potential vanilloid 5; expressed in late DCT (DCT2); Ca^{2+} resoprtion transporter; co-localizes with the calcium-binding protein calbindin-D_{28K}
TRPV6			transient receptor potential vanilloid 6; expressed in late DCT (DCT2); Ca^{2+} resoprtion transporter
Apical Membrane Efflux to Tubular Lumen			
SLC4A8	NDCBE: Na^+-driven Cl^-/HCO_3^- exchanger	Type B	Cl^- efflux coupled to Na^+ and HCO_3^- reabsorption; protein is also identified as NBC3
SLC26A4	Pendrin	Type B	Cl^- uptake coupled to HCO_3^- efflux
SLC26A6		Type A	efflux of HCO_3^- in exchange for Cl^- reabsorption; also involved in oxalate and sulfate anion transport
SLC26A9		Principal	efflux of Cl^-

KCNJ1	ROMK: renal outer medullary potassium channel	Principal	K+ efflux to lumen; members of the KCNJ family of inwardly rectifying voltage-gated potassium channels are also identified a Kir channels with ROMK being Kir1.1 (three isoforms due to alternative splicing: Kir1.1a, Kir1.1b, and Kir1.1c); aldosterone activates ROMK by inducing its phosphorylation by SGK1 (serum/glucocorticoid regulated kinase 1) which results in potassium secretion; mutations in gene are the cause of Bartter syndrome type 2
RHCG	Rh blood group antigen C	Type A	the RHCG gene is also identified as the SLC42A3 gene; ammonia (NH3) efflux to urine; also present in the basolateral membrane for uptake of NH3 from the blood
V-ATPase	H^+-ATPase	Type A	H+ efflux to urine occurs via V-ATPase present in type A intercalated cells; multisubunit complex composed of a cytoplasmic catalytic (V1) complex of eight proteins and a transmembrane (V0) complex composed of at least five subunits; all subunits of the V0 and V1 complexes are encoded by different genes