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palpable mass best felt with the patient supine, usually in a thin patient but occasionally due to a very large protruding mass. Very large masses or multiple masses that are easily palpable may represent cystic diseases of the kidney, including PCKD or even a single cyst, versus a congenital ureteral pelvic obstruction. Other times, a renal cell carcinoma can present as anemia, possibly caused by hematuria, or as back pain asso ciated with metastatic lytic vertebral lesions. Metastases may involve the lungs and bone marrow as well. ■ ■IMAGING AND RENAL BIOPSY INDICATIONS For hematuric syndromes, imaging may provide valuable information, particularly in a patient who has heavy bleeding or blood clots in the urine. Renal pathology may be detected as an abdominal mass, as in the set ting of renal cell carcinoma, chronic UTO, or cystic diseases of the kidney including PCKD and simple cyst. If the patient has a known his tory of tubular sclerosis or the finding of skin fibroadenoma, one might identify a renal mass found on CT imaging as an angiomyolipoma. The renal ultrasound is efficacious in determining the size and sym metry of the kidneys and in excluding urinary obstruction. It is useful in detecting renal cysts or masses but less effective in kidney stone disease. Ultrasound is not as accurate a tool as a computed tomography (CT) scan for angiomyolipomas. The renal-limited noncontrast CT scan is the standard test for nephrolithiasis but carries the risk of accu mulative radiation. Magnetic resonance imaging (MRI) is often useful in evaluating and following renal masses, including renal cell carci noma. The patient with renal disease may develop a toxic complication of systemic sclerosis after receiving multiple gadolinium studies for MRI enhancement; new contrast agents to replace it are emerging. CT scans with high-osmolality iodinated contrast media, administered in large volumes, remain an important cause of AKI (contrast nephropa thy) in elderly male patients with vascular disease of the kidney, mul tiple myeloma, hepatic disease, extracellular fluid depletion, DM, or concurrent use of NSAIDs. The accompanied radiation is a concern for radiation exposure. Radioisotope scanning is useful in demonstrating the percentage of renal function coming from each kidney. Finally, in many of the diseases discussed above, diagnosis ultimately depends on renal biopsy and pathologic evaluation. ■ ■FURTHER READING Bhosale SJ, Kulkarni AP: Biomarkers in acute kidney injury. Indian J Crit Care Med 24:S90, 2020. Canki E et al: Urinary biomarkers in kidney disease. Clin Chim Acta 55:117798, 2024. Glassock RJ: Kidney biopsy is required for nephrotic syndrome with PLA2R+ and normal kidney function: Commentary. Kidney 360:894, 2020. Levey AS et al: Nomenclature for

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Cell Biology and

Physiology of the Kidney The kidney is one of the most highly differentiated organs in the body. At the conclusion of embryologic development, nearly 30 different cell types form a multitude of filtering capillaries and segmented nephrons enveloped by a dynamic interstitium. This cellular diversity modulates a variety of complex physiologic processes. Endocrine functions, the regulation of blood pressure and intraglomerular hemodynamics, solute and water transport, acid-base balance, and removal of drug metabolites are all accomplished by intricate mechanisms of renal response. This breadth of physiology hinges on the clever ingenuity of nephron architecture that evolved as complex organisms came out of water to live on land. EMBRYOLOGIC DEVELOPMENT Kidneys develop from intermediate mesoderm under the timed or sequential control of a growing number of genes, described in Fig. 320-1. The transcription of these genes are determined or guided by morphogenic cues, the orientation of cilia-derived planar cell polar ity, and the generational legacy of epigenetic marks that invite two ureteric buds to each penetrate bilateral metanephric blastema, where they induce primary mesenchymal cells to form early nephrons. The two ureteric buds emerge from posterior nephric ducts and mature into separate collecting systems that eventually form a renal pelvis and ureter. Induced mesenchyme undergoes mesenchymal epithelial transitions to form comma-shaped bodies at the proximal end of each ureteric bud leading to the formation of S-shaped nephrons that cleft and enjoin with penetrating endothelial cells derived from sprouting angioblasts. Under the influence of vascular endothelial growth factor A (VEGF-A), these penetrating cells form capillaries with surrounding mesangial cells that differentiate into a glomerular filter for plasma water and solute. The ureteric buds branch, and each branch produces a new set of nephrons. The number of branching events ultimately determines the total number of nephrons in each kidney. There are ~900,000 glomeruli in each kidney in normal-birth-weight adults and as few as 225,000 in low-birth-weight adults, with the latter producing numerous comorbid risks. CHAPTER 320 Cell Biology and Physiology of the Kidney Glomeruli evolve as complex capillary filters with fenestrated endo thelia under the guiding influence of VEGF-A and angiopoietin-1 secreted by adjacently developing podocytes. Epithelial podocytes facing the urinary space envelop the exterior basement membrane sup porting these

emerging endothelial capillaries. Podocytes are partially polarized and periodically slough into the urinary space by epithelialmesenchymal transition and, to a lesser extent, apoptosis, only to be replenished by migrating parietal epithelia from Bowman capsule. Impaired replenishment results in heavy proteinuria. Podocytes attach to the basement membrane by special foot processes and share a slitpore membrane with their neighbor. The slit-pore membrane forms a filter for plasma water and solute by the synthetic interaction of nephrin, annexin-4, CD2AP, FAT, ZO-1, P-cadherin, podocin, TRPC6, PLCE1, and Neph 1-3 proteins. Mutations in many of these proteins also result in heavy proteinuria. The glomerular capillaries are embed ded in a mesangial matrix shrouded by parietal and proximal tubular epithelia forming Bowman capsule. Mesangial cells have an embryonic lineage consistent with arteriolar or juxtaglomerular cells and contain contractile actin-myosin fibers. These mesangial cells make contact with glomerular capillary loops, and their local matrix holds them in condensed arrangement. Between nephrons lies the renal interstitium. This region forms a functional space surrounding glomeruli and their downstream tubules, which are home to resident and trafficking cells such as fibroblasts, dendritic cells, occasional lymphocytes, and lipid-laden macrophages. The cortical and medullary peritubular capillaries, which siphon off

Brn1 Dll1 Jag1 Lhx1 Wnt4 Emx2 Fgf8 Notch2 Notch1 Lgr5 S-shape Comma-shape Pax2 Gdnf/Ret Lhx1 Cited1 Six1 Itga8/Itgb1 Fgfr2 Hoxa11/Hoxd11 Foxd1 Slit2/Robo2 Wt1 Pretubular aggregation Ureteric bud induction and condensation Nephrogenesis FIGURE 320-1 Genes controlling renal nephrogenesis. A growing number of genes have been identified at various stages of glomerulotubular development in the mammalian kidney. The genes listed have been tested in various genetically modified mice, and their location corresponds to the classical stages of kidney development postulated by Saxen in 1987. solute and water following tubular reclamation of glomerular filtrate, are also part of the interstitial fabric as well as a web of connective tissue that supports the kidney’s emblematic architecture of folding tubules. The relational precision of these structures determines the unique physiology of the kidney. PART 9 Disorders of the Kidney and Urinary Tract Each nephron is partitioned during embryologic development into a proximal tubule, descending and ascending limbs of the loop of Henle, distal tubule, and the collecting duct. These classic tubular segments build from subsegments lined by highly unique epithelia serving regional physiology. All nephrons have the same structural components, but there are two types whose structures depend on their location within the kidney. The majority of nephrons are cortical, with glomeruli located in the mid-to-outer cortex. Fewer nephrons are juxtamedullary, with glomeruli at the boundary of the cortex and outer medulla. Cortical nephrons have short loops of Henle, whereas juxtamedullary nephrons have long loops of Henle. There are critical differences in blood supply as well. The peritubular capillaries surrounding cortical nephrons are shared among adjacent nephrons. By contrast, juxtamedullary nephrons depend on indi vidual capillaries called vasa recta that run alongside the long loops of Henle. Cortical nephrons perform most of the glomerular filtration because there are more of them and because their afferent arterioles are larger than their respective efferent arterioles. The juxtamedul lary nephrons, with longer loops of Henle, create an osmotic gradient for concentrating urine. How developmental instructions specify the differentiation of all these unique epithelia among various tubular segments is still unknown. DETERMINANTS AND REGULATION OF GLOMERULAR FILTRATION Renal blood flow normally drains ~20% of the cardiac output, or 1000 mL/min. Blood reaches each nephron through the afferent arte riole leading into a glomerular capillary where ultrafiltration forms the tubular fluid. The distal ends of the glomerular capillaries coalesce to form an efferent arteriole leading to the first segment of a second capillary network (cortical peritubular capillaries or medullary vasa recta) surrounding

the tubules (Fig. 320-2A). Thus, nephrons have two capillary beds arranged in a series separated by the efferent arteriole that regulates the hydrostatic pressure in both capillary beds. The distal capillaries empty into small venous branches that coalesce into larger veins to eventually form the renal vein. The hydrostatic pressure gradient across the glomerular capillary wall is the primary driving force for glomerular filtration. Oncotic pressure within the capillary lumen, determined by the concentration of unfiltered plasma proteins, partially offsets the hydrostatic pressure gradient and opposes filtration. As the oncotic pressure rises along the length of the glomerular capillary, the driving force for filtration

Hnf1b VEGF-A/Kdr (Flk-1) Tcf21 Foxc2 Lmx1b Itga3/Itgb1 Pdgfb/Pdgfbr Cxcr4/Cxcl12 Nphs1 Nck1/Nck2 Cd36 CD2AP
Neph1 Nphs2 Lamb2 Capillary loop Mature glomerulus falls to zero en route to the efferent arteriole. Approximately 20% of the renal plasma flow is filtered into Bowman space, and the ratio of glomerular filtration rate (GFR) to renal plasma flow determines the filtration fraction. Several factors, mostly hemodynamic, contribute to the regulation of filtration under physiologic conditions. Although glomerular filtration is affected by renal artery pressure, this relationship is not linear across the range of physiologic blood pressures due to autoregulation of GFR. Autoregulation of glomeru lar filtration is the result of three major factors that modulate either afferent or efferent arteriolar tone; these include an autonomous vaso reactive (myogenic) reflex in the afferent arteriole, tubuloglomerular feedback (TGF), and angiotensin II–mediated vasoconstriction of the efferent arteriole. The myogenic reflex is a first line of defense against fluctuations in renal blood flow. Acute changes in renal perfusion pres sure evoke reflex constriction or dilatation of the afferent arteriole in response to rising or falling pressure, respectively. This phenomenon helps protect the glomerular capillary from sudden changes in systolic pressure. TGF changes the rate of filtration and tubular flow by reflex vaso constriction or dilatation of the afferent arteriole. TGF is mediated by specialized cells in the thick ascending limb of the loop of Henle called the macula densa that act as sensors of solute concentration and tubular fluid flow rate. With high tubular flow rates, a proxy for an inappropriately high filtration rate, greater solute delivery to the macula densa (Fig. 320-2B) evokes vasoconstriction of the afferent arteriole, causing GFR to return toward normal. One component of the soluble signal from the macula densa is adenosine triphosphate (ATP) released by the cells during increased NaCl reabsorption. ATP is metabolized in the extracellular space to generate adenosine, a potent vasoconstrictor of the afferent arteriole. During conditions associated with a fall in filtration rate, a lower rate of solute delivery to the macula densa attenuates TGF, allowing afferent arteriolar dilatation and restor ing GFR to normal levels. Angiotensin II and reactive oxygen species enhance TGF, whereas nitric oxide (NO) blunts TGF. A distinct feed back mechanism may exist between the connecting tubule and GFR in which high Na^+ delivery evokes afferent arteriolar dilation possibly mediated by prostaglandins. The third component underlying autoregulation of GFR involves angiotensin II. During states of reduced renal blood flow, renin is released from granular cells within the wall of the afferent arteriole near the macula densa in a region called the juxtaglomerular apparatus (Fig. 320-2B). Renin, a proteolytic enzyme, catalyzes the conversion of angiotensinogen to angiotensin I, which is subsequently converted to angiotensin II by angiotensin-converting enzyme (ACE) (Fig. 320-2C). Angiotensin II evokes vasoconstriction of the efferent arteriole, and the resulting increased glomerular hydrostatic pressure elevates GFR to normal levels.

Peritubular Proximal convoluted tubule capillaries Efferent arteriole Efferent arteriole Distal convoluted tubule Bowman capsule Glomerulus Afferent arteriole Thick ascending limb Proximal tubule Collecting duct B Peritubular venules A Angiotensinogen Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu - Val-Ile-His Angiotensin I Asp-Arg-Val-Tyr-Ile-His-Pro-Phe - His-Leu Angiotensin II Asp-Arg-Val-Tyr-Ile-His-Pro-Phe Angiotensin (I-VII) Asp-Arg-Val-Tyr-Ile-His-Pro C FIGURE 320-2 Renal microcirculation and the renin-angiotensin system. A. Diagram illustrating relationships of the nephron with glomerular and peritubular capillaries. B. Expanded view of the glomerulus with its juxtaglomerular apparatus including the macula densa and adjacent afferent arteriole. C. Proteolytic processing steps in the generation of angiotensins. MECHANISMS OF RENAL

TUBULAR TRANSPORT The renal tubules are composed of highly differentiated epithelia that vary in morphology and function along the nephron (Fig. 320-3). The cells lining the various tubular segments form monolayers connected to one another by a specialized region of the adjacent lateral membranes called the tight junction. Tight junctions form an occlusive barrier that separates the lumen of the tubule from the interstitial spaces surrounding the tubule and also apportions the cell membrane into discrete domains: the apical membrane facing the tubular lumen and the basolateral membrane facing the interstitium. This regionalization allows cells to allocate membrane proteins and lipids asymmetrically. Owing to this feature, renal epithelial cells are said to be polarized. The asymmetric assignment of membrane proteins, especially proteins mediating transport pro cesses, provides the machinery for directional movement of fluid and solutes by the nephron. ■ ■EPITHELIAL SOLUTE TRANSPORT There are two types of epithelial transport. Movement of fluid and solutes sequentially across the apical and basolateral cell membranes

Extraglomerular mesangial cells Glomerulus Macula densa Afferent arteriole Renin-secreting granular cells Proximal tubule Thick ascending limb CHAPTER 320 Renin Cell Biology and Physiology of the Kidney ACE ACE2 (or vice versa) mediated by transporters, channels, or pumps is called cellular transport. By contrast, movement of fluid and solutes through the narrow passageway between adjacent cells is called paracellular transport. Paracellular transport occurs through tight junctions, indi cating that they are not completely “tight” or occlusive. Indeed, some epithelial cell layers allow rather robust paracellular transport to occur (leaky epithelia), whereas other epithelia have more restrictive tight junctions (tight epithelia). In addition, because the ability of ions to flow through the paracellular pathway determines the electrical resistance across the epithelial monolayer, leaky and tight epithelia are also referred to as low- or high-resistance epithelia, respectively. The proximal tubule contains leaky epithelia, whereas distal nephron segments, such as the collecting duct, contain tight epithelia. Leaky epithelia are most well suited for bulk fluid reabsorption, whereas tight epithelia allow for more refined control and regulation of transport. ■ ■MEMBRANE TRANSPORT Cell membranes are composed of hydrophobic lipids that repel water and aqueous solutes. The movement of solutes and water across cell membranes is made possible by discrete classes of integral membrane

proteins, including channels, pumps, and transporters. These different mechanisms mediate specific types of transport activities, including active transport (pumps), passive transport (channels), facilitated diffusion (transporters), and secondary active transport (cotransporters). Active transport requires metabolic energy generated by the hydrolysis of ATP. Active transport pumps are ion-translocating ATPases, including the ubiquitous Na+/K+-ATPase, the H+-ATPases,

and Ca2+-ATPases. Active transport creates asymmetric ion concentrations across a cell membrane and can move ions against a chemical gradient. The poten tial energy stored in a concentration gradient of an ion such as Na+ can be used to drive transport through other mechanisms (secondary active transport). The movement of solutes through a membrane protein by simple diffusion is called passive transport. This activity is mediated by channels created by selectively permeable membrane proteins, and it allows solute or water to move across a membrane driven by favorable concentration gradients or electrochemical potential. Facilitated diffu sion is a specialized type of passive transport mediated by simple trans porters called carriers or uniporters. For example, hexose transporters such as GLUT2 mediate glucose transport by tubular cells. These transporters are driven by the concentration gradient for glucose that is highest in extracellular fluids and lowest in the cytoplasm due to rapid metabolism. Many other transporters operate by translocating two or more ions/solutes in concert either in the same direction (symporters or cotransporters) or in opposite directions (antiporters or exchangers) across the cell membrane. The movement of two or more ions/solutes may produce no net change in the balance of electrostatic charges across the membrane (electroneutral), or a transport event may alter the balance of charges (electrogenic). Several inherited disorders of renal tubular solute and water transport occur as a consequence of mutations

PART 9 Disorders of the Kidney and Urinary Tract CORTEX Macula densa Cortical collecting duct Distal convoluted tubule Proximal tubule Bowman capsule Vein Artery Connecting tubule SGLT2 inhibitors MEDULLA Loop of Henle: Thin descending limb Thick ascending limb Thin ascending limb Inner medullary collecting duct A FIGURE 320-3 Transport activities of the major nephron segments. Representative cells from five major tubular segments are illustrated with the lumen side (apical membrane) facing left and interstitial side (basolateral membrane) facing right. A. Overview of entire nephron. B. Proximal tubular cells. C. Typical cell in the thick ascending limb of the loop of Henle. D. Distal convoluted tubular cell. E. Cortical collecting duct principal cell. F. Cortical collecting duct type A and type B intercalated cells. G. Typical cell in the inner medullary collecting duct. The major membrane transporters, channels, and pumps are drawn with arrows indicating the direction of solute or water movement. For some events, the stoichiometry of transport is indicated by numerals preceding the solute. Targets for major diuretic agents are labeled. The actions of hormones are illustrated by arrows with plus signs for stimulatory effects and lines with perpendicular ends for inhibitory events. The dashed line indicates water impermeability of cell membranes in the thick ascending limb and distal convoluted tubule.

in genes encoding a variety of channels, transporter proteins, and their regulators (Table 320-1). The rate of tubular fluid flow through the nephron is highly variable, for which reason ion transport needs to be adjusted accordingly. Renal epithelial cells have the ability to monitor tubular fluid flow by mecha nisms involving cellular structures (apical microvilli, primary cilium) or mechanosensing ion channels. Tubular transport is regulated in response to changes in fluid flow through changes in intracellular Ca2+ or by purinergic receptor-mediated signal transduction. SEGMENTAL NEPHRON FUNCTIONS Each anatomic segment of the nephron has unique characteristics and specialized functions enabling selective transport of solutes and water (Fig. 320-3A). Through sequential events of reabsorption and secretion along the nephron, tubular fluid is progressively conditioned into urine. Knowledge of the major tubular mechanisms responsible for solute and water transport is critical for understanding hormonal regulation of kidney function and the pharmacologic manipulation of renal excretion. PROXIMAL TUBULE The proximal tubule is responsible for

reabsorbing ~60% of filtered NaCl and water, as well as ~90% of filtered bicarbonate and most critical nutrients such as glucose and amino acids. The proximal tubule uses both cellular and paracellular transport mechanisms. The apical membrane of proximal tubular cells has an expanded surface area available for reabsorption created by a dense array of microvilli called the brush border, and leaky tight junctions enable high-capacity fluid reabsorption. PROXIMAL TUBULE Lumen Interstitium Apical Basolateral HPO4 + H Na H 3Na 2K H2O H2PO4 Na Phosphate Na Glucose Glucose Na Amino acids Amino acids H2O, solutes Na H 3Na 2K NH4 Formic acid NH3 Cl K HCO3 + H
H Cl Formate Na 3HCO3 H2CO3 H2CO3 carbonic anhydrase carbonic anhydrase H2O + CO2 CO2 B

THICK ASCENDING LIMB Lumen Interstitium Loop diuretics 3Na Na K 2Cl 2K Cl K Ca H2O + – Ca, Mg C DISTAL CONVOLUTED TUBULE Lumen Interstitium Thiazides 3Na Na Cl 2K Cl Mg Ca 3Na Ca H2O D CORTICAL COLLECTING DUCT Lumen Interstitium Amiloride Principal cell Na 3Na 2K + + Spironolactone Eplerenone K Aldosterone + + Vasopressin + + H2O H2O E FIGURE 320-3 (Continued) Solute and water pass through these tight junctions to enter the lateral intercellular space where absorption by the peritubular capil laries occurs. Bulk fluid reabsorption by the proximal tubule is driven by high oncotic pressure and low hydrostatic pressure within the peri tubular capillaries. Cellular transport of most solutes by the proximal tubule is coupled to the Na+ concentration gradient established by the activity of a basolateral Na+/K+-ATPase (Fig. 320-3B). This active transport mechanism maintains a steep Na+ gradient by keep ing intracellular Na+ concentrations low. Solute reabsorption from

CORTICAL COLLECTING DUCT Type A intercalated cell Lumen Interstitium 3Na 2K H carbonic anhydrase H K HCO3 Cl Type B intercalated cell 3Na 2K carbonic anhydrase CHAPTER 320 HCO3 Cl H F Cell Biology and Physiology of the Kidney INNER MEDULLARY COLLECTING DUCT Lumen Interstitium ANP Na 3Na K 2K Vasopressin Urea + + H2O H2O G the tubular lumen is coupled to the Na+ gradient by Na+-dependent transporters such as Na+-glucose and Na+-phosphate cotransporters present in apical membranes. In addition to the paracellular route, water reabsorption also occurs through the cellular pathway enabled by constitutively active water channels (aquaporin-1) present on both apical and basolateral membranes. Proximal tubular cells reclaim nearly all filtered bicarbonate by a mechanism dependent on carbonic anhydrases. Filtered bicarbonate is first titrated by protons delivered to the lumen mainly by apical

TABLE 320-1 Inherited Disorders Affecting Renal Tubular Ion and Solute Transport DISEASE OR SYNDROME PROTEIN (GENE) OMIMa Disorders Involving the Proximal Tubule Proximal renal tubular acidosis Sodium bicarbonate cotransporter (SLC4A4, 4q21)

Fanconi-Bickel syndrome Glucose transporter, GLUT2 (SLC2A2, 3q26.2)

Isolated renal glycosuria Sodium glucose cotransporter (SLC5A2, 16p11.2)

Cystinuria Type I Cystine, dibasic and neutral amino acid transporter (SLC3A1, 2p16.3)

Non-type I Amino acid transporter, light subunit (SLC7A9, 19q13.1)

Lysinuric protein intolerance Amino acid transporter (SLC7A7, 4q11.2)

Dicarboxylic aminoaciduria Glutamate transporter (SLC1A1, 9q24.2)

Hartnup disorder Neutral amino acid transporter (SLC6A19, 5p15.33)

Hypophosphatemic nephrolithiasis/osteoporosis 1 Sodium phosphate cotransporter (SLC34A1, 5q35.3)

Hereditary hypophosphatemic rickets with hypercalcemia Sodium phosphate cotransporter (SLC34A3, 9q34)

Renal hypouricemia Type 1 Urate-anion exchanger (SLC22A12, 11q13)

Type 2 Urate transporter, GLUT9 (SLC2A9, 4p16.1)

Dent’s disease Chloride channel, ClC-5 (CLCN5, Xp11.22)

X-linked recessive nephrolithiasis with renal failure Chloride channel, ClC-5 (CLCN5, Xp11.22)

PART 9 Disorders of the Kidney and Urinary Tract X-linked recessive hypophosphatemic rickets Chloride channel, ClC-5 (CLCN5, Xp11.22)

Disorders Involving the Loop of Henle Bartter’s syndrome Type 1 Sodium, potassium chloride cotransporter (SLC12A1, 15q21.1)

Type 2 Potassium channel, ROMK (KCNJ1, 11q24)

Type 3 Chloride channel, ClC-Kb (CLCNKB, 1p36)

with sensorineural deafness Chloride channel accessory subunit, Barttin (BSND, 1p31)

Autosomal dominant hypocalcemia with Bartter-like syndrome Calcium-sensing receptor (CASR, 3q13.33)

Familial hypocalciuric hypercalcemia Calcium-sensing receptor (CASR, 3q13.33)

Familial hypomagnesemia type 3 Claudin-16 (CLDN16, 3q27)

Familial hypomagnesemia type 5 Claudin-19 (CLDN19, 1p34.2)

Isolated renal magnesium loss Sodium potassium ATPase, γ1-subunit (ATP1G1, 11q23)

Disorders Involving the Distal Tubule and Collecting Duct Gitelman syndrome Sodium chloride cotransporter (SLC12A3, 16q13)

Primary hypomagnesemia with secondary hypocalcemia Melastatin-related transient receptor potential cation channel 6 (TRPM6, 9q22)

Pseudoaldosteronism (Liddle’s syndrome) Epithelial sodium channel β and γ subunits (SCNN1B, SCNN1G, 16p12.1)

Recessive pseudohypoaldosteronism type 1 Epithelial sodium channel, α, β, and γ subunits (SCNN1A, 12p13; SCNN1B, SCNN1G, 16pp12.1)

Pseudohypoaldosteronism type 2 (Gordon’s hyperkalemia-hypertension syndrome) Kinases WNK-1, WNK-4 (WNK1, 12p13; WNK4, 17q21.31)

X-linked nephrogenic diabetes insipidus Vasopressin V2 receptor (AVPR2, Xq28)

EAST/SeSAME syndrome Potassium channel Kir4.1 (KCNJ10, 1q23.2)

Nephrogenic diabetes insipidus (autosomal) Water channel, aquaporin-2 (AQP2, 12q13)

Distal renal tubular acidosis autosomal dominant Anion exchanger-1 (SLC4A1, 17q21.31)

autosomal recessive Anion exchanger-1 (SLC4A1, 17q21.31)

with neural deafness Proton ATPase, β1 subunit (ATP6V1B1, 2p13.3)

with normal hearing Proton ATPase, 116-kD subunit (ATP6V0A4, 7q34)

aOnline Mendelian Inheritance in Man database (https://www.ncbi.nlm.nih.gov/omim). membrane Na+/H+ exchange. The resulting carbonic acid (H2CO3) is metabolized by brush border carbonic anhydrase to water and carbon dioxide. Dissolved carbon dioxide then diffuses into the cell, where it is enzymatically hydrated by cytoplasmic carbonic anhydrase to re-form carbonic acid. Finally, intracellular carbonic acid dissociates into free protons and bicarbonate anions, and bicarbonate exits the cell through a basolateral Na+/HCO3 − cotransporter. This process is saturable, which can result in renal bicarbonate excretion when plasma levels exceed the physiologically normal range (24–26 meq/L). Carbonic anhydrase

inhibitors such as acetazolamide block proximal tubule bicarbonate reabsorption and are useful for alkalinizing the urine. The proximal tubule contributes to acid secretion by two mechanisms involving the titration of the urinary buffers ammonia (NH3) and phos phate. Renal NH3 is produced by glutamine metabolism in the proximal tubule. Subsequent diffusion of NH3 out of the proximal tubular cell enables trapping of H+, which is secreted by apical Na+/H+ exchange, in the lumen as ammonium ion (NH4 +). Cellular K+ levels inversely modu late proximal tubular ammoniagenesis, and in the setting of high serum

K+ from hypoaldosteronism, reduced ammoniagenesis promotes type IV renal tubular acidosis. Filtered hydrogen phosphate ion (HPO4 2−) is also titrated in the proximal tubule by secreted H+ to form H2PO4 −, and this reaction constitutes a major component of the urinary buffer referred to as titratable acid. Most filtered phosphate ion is reabsorbed by the proximal tubule through a sodium-coupled cotransport process that is regulated by parathyroid hormone (PTH). Chloride is poorly reabsorbed throughout the first segment of the proximal tubule, and a rise in Cl− concentration counterbalances the removal of bicarbonate anion from tubular fluid. In later proxi

mal tubular segments, cellular Cl− reabsorption is initiated by apical exchange of cellular formate for higher luminal concentrations of Cl−. Once in the lumen, formate anions are titrated by H+ (provided by Na+/H+ exchange) to generate neutral formic acid, which can diffuse passively across the apical membrane back into the cell where it dis sociates a proton and is recycled. Basolateral Cl− exit is mediated by a K+/Cl− cotransporter. Reabsorption of glucose is nearly complete by the end of the proxi mal tubule. Cellular transport of glucose is mediated by apical Na+- glucose cotransport coupled with basolateral, facilitated diffusion by a glucose transporter. This process is also saturable, leading to glycosuria when plasma levels exceed 180–200 mg/dL, as seen in untreated dia betes mellitus. Inhibitors of the Na+-glucose cotransporter SLGT2 in proximal tubules block glucose reabsorption and lower blood glucose, which has therapeutic benefits in diabetes mellitus and chronic dia betic kidney disease. The proximal tubule possesses specific transporters capable of secret ing a variety of organic acids (carboxylate anions) and bases (mostly primary amine cations). Organic anions transported by these systems include several protein-bound drugs not filtered at the glomerulus (penicillins, cephalosporins, salicylates, and others). Organic cations secreted by the proximal tubule include various biogenic amine neu rotransmitters (dopamine, acetylcholine, epinephrine, norepinephrine, and histamine) and creatinine. The ATP-dependent transporter P-gly coprotein encoded by ABCB1 is expressed in brush border membranes and secretes several medically important drugs, including cyclosporine, digoxin, tacrolimus, and various cancer chemotherapeutic agents. Certain drugs such as cimetidine and trimethoprim compete with endogenous compounds for transport by the organic cation pathways. Although these drugs elevate serum creatinine levels, there is no actual change in GFR in this setting. Calcium and phosphorus homeostasis depends on normal function ing of the proximal tubule. Approximately 60–70% of filtered calcium and ~85% of filtered phosphorus (in the form of inorganic phosphate) are reabsorbed by the proximal tubule. Whereas calcium reabsorp tion is mostly by passive diffusion through the paracellular route, phosphate reabsorption is mediated by sodium-coupled cotransport. In addition to direct reabsorption, the proximal tubule contributes to systemic mineral balance by participating in specific endocrine path ways. Circulating 25-hydroxy vitamin D (calcidiol) is bioactivated by proximal tubular 1α-hydroxylase to produce 1,25-di-hydroxy vitamin D (calcitriol), the most active form of the hormone, which acts on the small intestine to promote calcium absorption. Phosphate balance is affected by circulating fibroblast growth hormone 23 (FGF23), a bone-derived hormone that interacts with its receptor (FGFR1) and co-receptor (Klotho) on proximal tubular cells to suppress sodiumphosphate cotransport and promote renal phosphate excretion. PTH stimulates proximal tubular 1α-hydroxylation of vitamin D, whereas it suppresses sodium-phosphate cotransport. Derangements in PTH and FGF23 account for abnormal calcium and phosphate balance in chronic kidney disease. The proximal tubule, through distinct classes of Na+-dependent and Na+-independent transport systems, reabsorbs amino acids efficiently. These transporters are specific for different groups of amino acids. For example, cystine, lysine, arginine, and ornithine are transported by a system comprising two proteins encoded by the SLC3A1 and SLC7A9 genes. Mutations in either SLC3A1 or SLC7A9 impair reabsorption of these amino acids and cause the disease cystinuria. Peptide hormones, such as insulin and growth hormone, β2-microglobulin, and other

small proteins, are taken up by the proximal tubule through a process of absorptive endocytosis and are degraded in acidified endocytic lysosomes. Acidification of these vesicles depends on a multi-subunit vacuolar H+-ATPase and a separate Cl−/H+ exchanger encoded by CLCN5. Impaired acidification of endocytic vesicles because of CLCN5 patho genic variants causes low-molecular-

weight proteinuria in Dent’s disease.

LOOP OF HENLE The loop of Henle consists of three major segments: descending thin limb, ascending thin limb, and ascending thick limb. Approximately 15–25% of filtered NaCl is reabsorbed in the loop of Henle, mainly by the thick ascending limb. The loop of Henle has an important role in urinary concentration by contributing to the generation of a hyper tonic medullary interstitium in a process called countercurrent multipli cation. The loop of Henle is the site of action for the most potent class of diuretic agents (loop diuretics) and also contributes to reabsorption of calcium and magnesium ions. The descending thin limb is highly water permeable owing to dense expression of constitutively active aquaporin-1 water channels. By contrast, water permeability is negligible in the ascending thin and thick limbs. In the thick ascending limb, there is a high level of secondary active NaCl transport enabled by the Na+/K+/2Cl− cotrans porter on the apical membrane in series with basolateral Cl− channels and Na+/K+-ATPase (Fig. 320-3C). The Na+/K+/2Cl− cotransporter is the molecular target for loop diuretics. Tubular fluid K+ is the limit ing substrate for this cotransporter (tubular concentration of K+ is similar to plasma, ~4 meq/L), but transporter activity is maintained by K+ recycling through an apical potassium channel. The cotrans porter also enables reabsorption of NH4 CHAPTER 320 Cell Biology and Physiology of the Kidney

- in lieu of K+, and this leads to accumulation of both NH4
- and NH3 in the medullary interstitium. An inherited disorder of the thick ascending limb, Bartter’s syndrome, is a salt-wasting renal disease associated with hypokalemia and meta bolic alkalosis. Loss-of-function mutations in one of five distinct genes encoding components of the Na+/K+/2Cl− cotransporter (NKCC2), apical K+ channel (KCNJ1), basolateral Cl− channel (CLCNKB, BSND), or calcium-sensing receptor (CASR) can cause Bartter’s syndrome. Potassium recycling also contributes to a positive electrostatic charge in the lumen relative to the interstitium that promotes divalent cation (Mg2+ and Ca2+) reabsorption through a paracellular pathway. A Ca2+-sensing, G protein–coupled receptor (CaSR) on basolateral membranes regulates NaCl reabsorption in the thick ascending limb through dual signaling mechanisms using either cyclic AMP or eicosanoids. This receptor enables a steep relationship between plasma Ca2+ levels and renal Ca2+ excretion. Loss-of-function muta tions in CaSR cause familial hypercalcemic hypocalciuria because of a blunted response of the thick ascending limb to extracellular Ca2+. Mutations in CLDN16 encoding paracellin-1, a transmembrane protein located within the tight junction complex, leads to familial hypomagnesemia with hypercalciuria and nephrocalcinosis, suggest ing that the ion conductance of the paracellular pathway in the thick limb is regulated. The loop of Henle contributes to urine-concentrating ability by establishing a hypertonic medullary interstitium that promotes water reabsorption by the inner medullary collecting duct located down stream in the nephron. Countercurrent multiplication produces a hypertonic medullary interstitium using two countercurrent systems: the loop of Henle (opposing descending and ascending limbs) and the vasa recta (medullary peritubular capillaries enveloping the loop). The countercurrent flow in these two systems helps maintain the hyper tonic environment of the inner medulla, but NaCl reabsorption by the thick ascending limb is the primary initiating event. Reabsorption of NaCl without water dilutes the tubular fluid and adds new osmoles to medullary interstitial fluid. Because the descending thin limb is highly water permeable, osmotic equilibrium occurs between the

descend ing limb tubular fluid and the interstitial space, leading to progressive solute trapping in the inner medulla. Maximum medullary interstitial osmolality also requires partial recycling of urea mediated by urea transporters in the inner medullary collecting duct.

DISTAL CONVOLUTED TUBULE The distal convoluted tubule reabsorbs ~5% of filtered NaCl. This seg ment is composed of a tight epithelium with little water permeability. The major NaCl-transporting pathway uses an apical membrane, electroneutral thiazide-sensitive Na+/Cl− cotransporter in tandem with basolateral Na+/K+-ATPase and Cl− channels (Fig. 320-3D). Apical Ca2+-selective channels (TRPV5) and basolateral Na+/Ca2+ exchange mediate calcium reabsorption in the distal convoluted tubule. Ca2+ reabsorption is inversely related to Na+ reabsorption and is stimulated by PTH. Blocking apical Na+/Cl− cotransport will reduce intracellular Na+, favoring increased basolateral Na+/Ca2+ exchange and passive api cal Ca2+ entry. Loss-of-function mutations of SLC12A3 encoding the apical Na+/Cl− cotransporter cause Gitelman syndrome, a salt-wasting disorder associated with hypokalemic alkalosis and hypocalciuria. Mutations in TRPM6 encoding Mg2+ permeable ion channels also cause familial hypomagnesemia with hypocalcemia. A molecular com plex of TRPM6 and TRPM7 proteins is critical for Mg2+ reabsorption in the distal convoluted tubule. Basolateral Mg2+ exit from these cells is postulated to involve Na+/Mg2+ exchange.

COLLECTING DUCT The collecting duct modulates the final composition of urine. The two major divisions, the cortical collecting duct and inner medullary collecting duct, contribute to reabsorbing ~4–5% of filtered Na+ and are important for hormonal regulation of salt and water balance. Cells in both segments of the collecting duct express vasopressin-regulated water channels (aquaporin-2 on the apical membrane, aquaporin-3 and -4 on the basolateral membrane). The antidiuretic hormone vaso pressin binds to the V2 receptor on the basolateral membrane and triggers an intracellular signaling cascade through G protein–mediated activation of adenylyl cyclase, which raises intracellular levels of cyclic AMP. This signaling cascade stimulates the insertion of water channels into the apical membrane of collecting duct cells to promote water per meability, water reabsorption, and production of concentrated urine. In the absence of vasopressin, collecting duct cells are water imper meable, and urine remains dilute. Nonpeptide V2 receptor blockers (vaptans) antagonize the antidiuretic effect of vasopressin and produce a water diuresis to treat symptomatic hyponatremia and can slow the progression of polycystic kidney disease. PART 9 Disorders of the Kidney and Urinary Tract The cortical collecting duct contains high-resistance epithelia with two cell types. Principal cells are the main water-reabsorbing, Na+-reabsorbing, and K+-secreting cells, and the site of action of aldosterone, K+-sparing diuretics, and mineralocorticoid receptor antagonists such as spironolactone and eplerenone. The other cells are type A and B intercalated cells. Type A intercalated cells mediate acid secretion and bicarbonate reabsorption also under the influence of aldosterone. Type B intercalated cells mediate bicarbonate secretion and acid reabsorption. Virtually all transport is mediated through the cellular pathway for both principal cells and intercalated cells. In principal cells, passive apical Na+ entry occurs through an amiloride-sensitive, epithelial Na+ channel (ENaC) with basolateral exit mediated by the Na+/ K+-ATPase (Fig. 320-3E). This Na+ reabsorptive process is tightly regulated by aldosterone and is physiologically activated by a variety of proteolytic enzymes that cleave extracellular domains of ENaC; plasmin in the tubular fluid of individuals affected by nephrotic syndrome, for example, activates ENaC, leading to Na+ retention. Aldosterone enters the cell across the basolateral membrane, binds to a

cytoplasmic mineralocorticoid receptor, and then translocates into the nucleus, where it modulates gene transcription, which potentiates Na+ reabsorption and K+ secretion. Activating mutations in ENaC increase Na+ reclamation and produce hypokalemia, hypertension, and metabolic alkalosis (Liddle's syndrome). The potassium-sparing diuretics amiloride and triamterene block ENaC, resulting in lower Na+ reabsorption. Principal cells secrete K+ through an apical membrane potassium channel. Several forces govern the secretion of K+. Most importantly, the high intracellular K+ concentration generated by Na+/K+-ATPase creates a favorable concentration gradient for K+ secretion into tubular

fluid. With reabsorption of Na+ without an accompanying anion, the tubular lumen becomes negative relative to the cell interior, creating a favorable electrical gradient for secretion of potassium. When Na+ reabsorption is blocked, the electrical component of the driving force for K+ secretion is blunted, and this explains lack of excess urinary K+ loss during treatment with potassium-sparing diuretics or min eralocorticoid receptor antagonists. K+ secretion is also promoted by aldosterone actions that potentiate regional Na+ transport, which favor more lumen electronegativity, and by increasing the number and activity of potassium channels. Fast tubular fluid flow rates that occur during volume expansion or diuretics acting "upstream" of the cortical collecting duct also promote K+ secretion, as does the presence of relatively nonreabsorbable anions (including bicarbonate and semi synthetic penicillins) that contribute to the lumen-negative potential. Off-target effects of certain antibiotics, such as trimethoprim and pentamidine, block ENaCs and predispose to hyperkalemia, especially when renal K+ handling is impaired for other reasons. Principal cells, as described below, also participate in water reabsorption in response to vasopressin. Intercalated cells do not participate in Na+ reabsorption but instead mediate acid-base balance. These cells perform two types of transport: active H+ transport mediated by H+-ATPase (proton pump) and Cl−/ HCO_3^- exchange. Intercalated cells arrange the two transport mecha nisms on opposite membranes to enable either acid or base secretion. Type A intercalated cells have an apical proton pump that mediates acid secretion and a basolateral Cl−/HCO_3^- anion exchanger for bicar bonate reabsorption (Fig. 320-3E). Aldosterone increases the number of H+-ATPase pumps, sometimes contributing to the development of metabolic alkalosis. Secreted H+ is buffered by NH_3 that has diffused into the collecting duct lumen from the surrounding interstitium. By contrast, type B intercalated cells have the Cl−/HCO_3^- exchanger on the apical membrane to mediate bicarbonate secretion while the proton pump resides on the basolateral membrane to enable H+ reabsorption. Under conditions of acidemia, the kidney preferentially uses type A intercalated cells to secrete the excess H+ and generate more HCO_3^-. The opposite is true in states of bicarbonate excess with alkalemia where the type B intercalated cells predominate. An extracellular pro tein called hensin mediates this adaptation. Inner medullary collecting duct cells share many similarities with principal cells of the cortical collecting duct. They have apical Na+ and K+ channels that mediate Na+ reabsorption and K+ secretion, respectively (Fig. 320-3F). Sodium reabsorption by inner medullary collecting duct cells is also inhibited by the natriuretic peptides atrial natriuretic peptide or renal natriuretic peptide (urodilatin); the same gene encodes both peptides but uses different posttranslational pro cessing of a common preprohormone to generate different proteins. Atrial natriuretic peptides are secreted by atrial myocytes in response to volume expansion, whereas urodilatin is secreted by renal tubular epithelia. Natriuretic peptides interact with either apical (urodilatin) or basolateral (atrial natriuretic peptides) receptors on inner medul lary collecting duct cells to stimulate guanylyl cyclase and raise levels of cytoplasmic cGMP. This effect in turn reduces the activity of the apical Na+ channel in these cells and attenuates net Na+

reabsorption, producing natriuresis. The inner medullary collecting duct transports urea out of the lumen, returning urea to the interstitium, where it contributes to the hypertonicity of the medullary interstitium. Urea is recycled by diffus ing from the interstitium into the descending and ascending limbs of the loop of Henle. HORMONAL REGULATION OF SODIUM AND WATER BALANCE The balance of solute and water in the body is determined by the amounts ingested, distributed to various fluid compartments, and excreted by skin, bowel, and kidneys. Tonicity, the osmolar state deter mining the volume behavior of cells in a solution, is regulated by water balance (Fig. 320-4A), and extracellular blood volume is regulated by Na+ balance (Fig. 320-4B). The kidney is a critical modulator of both physiologic processes.

Cell volume Cell membrane TB H2O Net water balance

- TB H2O TB Na+ + TB K+ pNa+ = Tonicity = = Effective osmoles TB H2O A Extracellular blood volume and pressure (TB Na+ + TB H2O + Vascular tone + Heart rate + Stroke volume) Net Na+ balance
- TB Na+ B FIGURE 320-4 Determinants of sodium and water balance. A. Plasma Na+ concentration is a surrogate marker for plasma tonicity. Tonicity is determined by the number of effective osmoles in the body divided by the total body H2O (TB H2O), which translates simply into the total body Na (TB Na+) and anions outside the cell separated from the total body K (TB K+) inside the cell by the cell membrane. Net water balance is determined by the integrated functions of thirst, osmoreception, Na reabsorption, vasopressin release, and the strength of the medullary gradient in the kidney, keeping tonicity within a narrow range of osmolality (~280 mosmol/L). When water metabolism is disturbed and total body water increases, hyponatremia, hypotonicity, and water intoxication occur; when total body water decreases, hypernatremia, hypertonicity, and dehydration occur. B. Extracellular blood volume and pressure are an integrated function of total body Na+ (TB Na+), total body H2O (TB H2O), vascular tone, heart rate, and stroke volume that modulates volume and pressure in the vascular tree of the body. This extracellular blood volume is determined by net Na balance under the control of taste, baroreception, habit, Na+ reabsorption, macula densa/tubuloglomerular feedback, and natriuretic peptides. When Na+ metabolism is disturbed and total body Na+ increases, edema occurs; when total body Na+ is decreased, volume depletion occurs. ADH, antidiuretic hormone; AQP2, aquaporin-2. ■ ■WATER BALANCE Tonicity depends on the variable concentration of effective osmoles inside and outside the cell causing water to move in either direction across its membrane. Classic effective osmoles, like Na+, K+, and their anions, are solutes trapped on either side of a cell membrane, where they collectively partition and obligate water to move and find equilibrium in proportion to retained solute. Normal tonicity (~280 mosmol/L) is rigorously defended by osmoregulatory mecha nisms that control water balance to protect tissues from inadvertent dehydration (cell shrinkage) or water intoxication (cell swelling), both of which impair cell function (Fig. 320-4A). The mechanisms that control osmoregulation are distinct from those governing extracellular volume, although there is some shared physiology in both processes. While cellular concentrations of K+ have a determinant role in any level of tonicity, the routine sur rogate marker for assessing clinical tonicity is the concentration of serum Na+. Any reduction in total body water, which raises the Na+ concentration, triggers a brisk sense of thirst and conservation of water by decreasing

renal water excretion mediated by release of vasopressin from the posterior pituitary. Conversely, a lower plasma Na+ concentration triggers more renal water excretion by suppressing the secretion of vasopressin. Whereas all cells expressing mechano sensitive TRPV1, 2, or 4 channels, among potentially other sensors, respond to changes in tonicity by altering their volume and Ca2+ concentration, only TRPV+ neuronal cells connected to the organum

Determinants Water intake Clinical result Thirst Osmoreception Custom/habit Hyponatremia Hypotonicity Water intoxication – TB H2O Hypernatremia Hypertonicity Dehydration Renal regulation ADH levels V2-receptor/AP2 water flow Medullary gradient Free water clearance Determinants Na+ intake Clinical result Taste Baroreception Custom/habit CHAPTER 320 Edema – TB Na+ Volume depletion Cell Biology and Physiology of the Kidney Renal regulation Na+ reabsorption Tubuloglomerular feedback Macula densa Atrial natriuretic peptides Fractional Na+ excretion vasculosum of the lamina terminalis are osmoreceptive. Only these cells, because of their neural connectivity and adjacency to a minimal blood-brain barrier, modulate the downstream release of vasopressin by the posterior lobe of the pituitary gland. Secretion is stimulated primarily by changing tonicity and secondarily by other nonosmotic signals such as variable blood volume, stress, pain, nausea, and some drugs. The release of vasopressin by the posterior pituitary increases linearly as plasma tonicity rises above normal, although this var ies, depending on the perception of extracellular volume (one form of cross-talk between mechanisms that regulate blood volume and osmolality). Changing the intake or excretion of water provides a means for adjusting plasma tonicity; thus, osmoregulation governs water balance. The kidneys contribute to maintaining water balance through the regulation of renal water excretion. The ability to concentrate urine to an osmolality exceeding that of plasma enables water conservation, whereas the ability to produce urine more dilute than plasma promotes excretion of excess water. For water to enter or exit a cell, the cell mem brane must express aquaporins. In the kidney, aquaporin-1 is consti tutively active in all water-permeable segments (e.g., proximal tubule, descending thin limb of the loop of Henle), whereas aquaporin-2, -3, and -4 in the collecting duct promote vasopressin-regulated water perme ability. Net water reabsorption is ultimately driven by the osmotic gradient between dilute tubular fluid and a hypertonic medullary interstitium.

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