can occur within the same nephron segment (e.g., early vs. late proximal tubule) or across different segments (e.g., proximal vs. distal nephron segments).

Secretion

Secretion is an ancient mode of excretion that is found in lower-order organisms. Although the human nephron is not primarily secretory in nature, a number of solutes are still handled by secretion. For example, the renal excretion of potassium (K^+) and hydrogen (H^+) ions is largely achieved by secretion. Many organic cations and anions are secreted by the proximal tubule, and so are many exogenous toxins such as xenobiotics. The secretion of creatinine by organic cation transporters in the proximal tubule is the reason why creatinine clearance overestimates GFR.

Integrated Models of Excretion

The modes of excretion are well coordinated in a precise, complex, and concerted fashion to effect excretion with exquisite accuracy (see Table 25-2). The kidney is capable of a large range of urinary tonicity (<50 to 1200 mOsm), depending on the need of the organism to excrete or conserve electrolyte-free water. Water is filtered at the glomerulus and is handled isotonically in the proximal tubule. At the lumen of the distal convoluted tubule, urine is maximally dilute as a consequence of low water permeability throughout the thick ascending limb of Henle. The subsequent fate of the urine determines whether there is electrolyte-free water excretion (dilute urine), achieved by low water permeability of the collecting duct, or electrolyte-free water conservation (concentrated urine), effected by the action of antidiuretic hormone (ADH), which renders the collecting tubule permeable to water.

Na^+ homeostasis basically occurs via filtration-reabsorption; it is regulated by changes in effective arterial blood volume (EABV) mediated by neurohormonal afferent signals that act directly on tubules. In the proximal tubule, Na^+ reabsorption is also regulated by peritubular physical factors. K^+ undergoes an interesting sequence in which the filtered load is largely reabsorbed in the proximal tubule and the thick ascending limb; the final determinant of excretion is secretion by the collecting duct, for which aldosterone and distal Na^+ delivery are major regulators.

Only Ca^{2+} that is not bound to plasma protein is filtered; it is reabsorbed largely via paracellular pathways in the proximal tubule and thick ascending limb and via transcellular pathways in the distal convoluted tubule.

A massive amount of bicarbonate (HCO_3^-) is filtered and must be reclaimed to forestall catastrophic acidosis. H^+ secretion provides the mechanism for HCO_3^- reclamation as well as acid excretion, with the H^+ being carried by urinary buffers such as ammonia.

Metabolic Function

The kidney is a major metabolic organ. It consumes a wide range of fuels, regulates plasma levels of metabolic substrates, and is a major source of gluconeogenesis. Metabolic substrates such as amino acids, glucose, organic anions, and fatty acids are converted to ATP, the universal energy unit for all cells (see Fig. 25-2A). ATP is directly hydrolyzed by transport proteins such as Na^+/K^+-ATPase to create a low intracellular Na^+ concentration ($[Na^+]$) and a negative interior cell voltage, thus translating the energy into chemical gradients. About 80% to 90% of the oxygen consumption of the kidney can be attributed to Na^+ transport. For example, a protein such as the Na^+-glucose cotransporter (see Fig. 25-2B) on the luminal membrane couples the movement of one Na^+ ion to one glucose molecule (carrying a net positive charge). The low cell $[Na^+]$ and negative voltage energize glucose uptake, allowing the proximal tubule to capture most of the filtered glucose that otherwise would be lost in the urine. In normal physiology, this glucose reclamation is beneficial.

The amount of filtered organic molecules far exceeds the metabolic consumption by the kidney. Very large amounts of organic metabolic substrates are passively filtered daily; these substrates are not meant to be excreted, but the high GFR and lack of retention at the glomerular capillaries obligate their presence in the glomerular urine. In the proximal tubule, the bulk of the filtered organic molecules are reclaimed from the urine and returned to the systemic circulation. Several thousands of millimoles of amino acids, glucose, and organic cations and anions are retrieved each day by the kidney from the urine.

The kidney rivals the liver as a gluconeogenic organ that sustains circulating blood glucose levels. Although there is no doubt that this is an critical physiologic function, there are no clinical examples of hypoglycemia stemming purely from lack of renal gluconeogenesis.

Endocrine Function

In addition to the prominent and more obvious roles in solute and water balance, the kidney also is an important endocrine organ. The autocrine and paracrine substances elaborated by the kidney are important for both intrarenal and systemic regulation. Although this subject is not addressed fully here, three of these substances are highlighted because they represent important pharmacologic targets (Table 25-3).

Renin

As the initiating component of the renin-angiotensin-aldosterone system (RAAS), renin is important for maintenance of the integrity of the circulation. The RAAS permits the kidney to have a constant GFR in the face of low and fluctuating salt intake, a property that is vital for terrestrial existence. Renin is produced by the JGA (see earlier discussion). Despite the benefits and importance of the RAAS in physiology, its activation in many disease states appears to be maladaptive and contributes to kidney and cardiovascular injury. Pharmacologic blockade of RAAS pathways at various levels has proved beneficial in animal disease models and human clinical studies, and agents to block RAAS signaling are now in clinical use, with others under development (see Table 25-3).

Vitamin D

1α-Hydroxylase (cytochrome P-450 isoenzyme 27B1) is found in the proximal tubule, where the major body defense for maintaining phosphate homeostasis is localized. Lesser expression of the same enzyme is also found in the rest of the nephron segments. The kidney is one of the most important organs for maintaining calcium and phosphate homeostasis, not just as the major controller of external balance but as an elaborator of systemic