A 60-year-old man with a history of heart disease is admitted to the hospital with congestive heart failure. He is stabilized and treated in the intensive care unit. His pulmonary edema and peripheral edema improve when furosemide (Lasix), a loop diuretic, is administered. The patient is discharged home with furosemide and other medications. He returns to his primary care physician 3 weeks after the hospitalization and complains of weakness, dizziness, and nausea. An electrolyte panel demonstrates hypokalemia, and he is started on supplemental potassium, with improvement of his symptoms.

◆ **How does a loop diuretic work?**

◆ **How do loop diuretics cause hypokalemia?**

◆ **What is the effect of aldosterone on sodium and potassium?**
ANSWERS TO CASE 23: LOOP OF HENLE, DISTAL TUBULE, AND COLLECTING DUCT

Summary: A 60-year-old man with congestive heart failure is treated with loop diuretics and subsequently develops hypokalemia.

◆ **Loop diuretics:** Act on the sodium-potassium-chloride cotransporter in the loop of Henle and decrease the reabsorption of sodium and water.

◆ **Hypokalemia with loop diuretics:** An increased flow rate through the late distal tubule and cortical collecting duct causes dilution of luminal potassium concentration and favors potassium secretion.

◆ **Effect of aldosterone on the reabsorption of sodium:** Increases the number of sodium channels in the luminal membrane, the number of sodium-potassium ATPase transporters, and the activity of Krebs cycle enzymes in the late distal tubule and cortical collecting duct.

**CLINICAL CORRELATION**

Loop diuretics such as furosemide are commonly used diuretic medications. Patients with congestive heart failure, cirrhosis, and pulmonary edema often are started on these medications. Their site of action is primarily on the sodium-potassium-chloride cotransporter (Na-K-Cl cotransporter) in the loop of Henle, hence the term loop diuretics. They ultimately decrease sodium and water reabsorption, resulting in diuresis. However, patients on loop diuretics are prone to hypokalemia. This expected side effect results because the increased flow rate through the distal tubule and cortical collecting duct causes a dilution decrease in the luminal potassium concentration and favors potassium secretion. Patients on diuretics often need to take potassium supplements. Hypokalemia presents clinically with muscle weakness, nausea, fatigue, dizziness, and intestinal ileus and, if potassium is low enough, may lead to coma and fatal cardiac arrhythmias. Not all diuretics lead to hypokalemia. Spironolactone is an antagonist of aldosterone, and amiloride acts on the sodium channel; both do not result in increased potassium loss. These two medications are examples of potassium-sparing diuretics.

**APPROACH TO LOOP OF HENLE, DISTAL TUBULE, AND COLLECTING DUCT**

Objectives

1. Know about reabsorption and secretion in the loop of Henle, distal tubule, and collecting duct.
2. Describe the effects of aldosterone on the distal tubule and collecting duct.
Definitions

**Loop diuretic:** A diuretic that inhibits the Na-K-Cl cotransporter in the thick ascending limb of the loop of Henle. An example is furosemide.

**Potassium-sparing diuretic:** A diuretic that acts by inhibiting sodium reabsorption and potassium secretion in the late distal tubule and cortical collecting duct, thereby inhibiting the loss of potassium.

**Aldosterone:** A mineralocorticoid hormone that stimulates the reabsorption of sodium from and the secretion of potassium into the late distal tubule and cortical collecting duct.

**DISCUSSION**

Of the 30% to 40% of the fluid filtered at the glomerulus that is not reabsorbed by the proximal tubule, most is reabsorbed by the loop of Henle, distal tubule, and collecting duct system, except for a small percentage (typically <1%-2%) that normally is tightly regulated to maintain a balance of body fluids and electrolytes. The loop of Henle plays a particularly central role in giving the kidneys the ability to both concentrate and dilute urine, providing the foundation for both osmotic balance and volume balance.

The loop of Henle consists of the thin descending limb, the thin ascending limb, and the thick ascending limb, which ends at the macula densa (adjacent to its own glomerulus). The segments reabsorb 25% to 30% of the filtered NaCl, primarily in the thick ascending limb, with a smaller fraction of water, thereby rendering the medullary interstitial fluid hypertonic and the fluid leaving the thick ascending limb hypotonic, a condition that is necessary for excreting a urine with a variable osmolality. This occurs by a mechanism referred to as the countercurrent multiplier system that is dependent on the transport properties of the various segments: high water permeability and low NaCl permeability of the thin descending limb, high NaCl permeability and low water permeability of the thin ascending limb, and low water permeability with active reabsorption of Na⁺, along with Cl⁻, of the thick ascending limb, the segment that is the driving force for the whole process. Active reabsorption of Na⁺, along with Cl⁻, by the thick ascending limb renders the medullary interstitial fluid hypertonic, causing reabsorption of water from the descending limb. However, relatively more NaCl than water is transported into the interstitium, and so the medullary interstitium becomes hypertonic. With the countercurrent flow of fluid down the descending limb and up the ascending limb, a vertical amplification of the interstitial hypertonicity develops, increasing from approximately 290 mOsmol/kg at the corticomедullary junction to as high as 1200 to 1400 mOsmol/kg near the tip of the papilla (see the references at the end of this case for more detail). Conversely, fluid leaving the thick ascending limb is hypotonic (approximately 100 mOsmol/kg). An essential transport process for Na⁺ and Cl⁻ reabsorption in the thick ascending limb is the entry step at the luminal membrane:
a coupled cotransporter, the Na\(^+\)-K\(^+\)-Cl\(^-\) cotransporter, that transports 1 Na\(^+\), 1 K\(^+\), and 2 Cl\(^-\) together across the luminal cell membrane in an electroneutral fashion.

Modulating or inhibiting this cotransporter directly regulates net transport of NaCl across the cell, thereby regulating the magnitude of the medullary interstitial hypertonicity. In addition, because of this cotransporter, K\(^+\) that enters the cell can diffuse back across the luminal membrane via a luminal membrane K\(^+\) channel (see Figure 23-1) while Cl\(^-\) that enters diffuses across the basolateral membrane via selective Cl\(^-\) channels, leading to Cl\(^-\) reabsorption along with Na\(^+\). The K\(^+\) and Cl\(^-\) diffusion processes set up a lumen-positive membrane potential, as shown in the figure. Because the paracellular pathway through the tight junctions is more selective for cations, the lumen-positive potential arising from the cellular transport processes will lead to passive reabsorption of Na\(^+\) between the cells as part of the process of NaCl reabsorption in this segment. As fluid leaves the loop of Henle, it enters the **distal convoluted tubule** in the cortex. Here Na\(^+\), along with Cl\(^-\), is reabsorbed actively, with the entry of Na\(^+\) across the luminal membrane being coupled to Cl\(^-\) by a thiazide-sensitive NaCl cotransporter. The water permeability of the segment is relatively low so that little water is reabsorbed by this segment.

Fluid passes from the distal convoluted tubule into the late **distal tubule** (connecting tubule/initial collecting tubule) and on into the **cortical collecting duct and medullary collecting duct segments**. Na\(^+\) is actively reabsorbed by

![Figure 23-1. Thick ascending limb cell. Furosemide affects Na\(^+\), K\(^+\), and Cl\(^-\) transport.](image)
the connecting tubule cells and by the principal cells of the initial and cortical collecting duct and, to a much lesser extent, by the principal cells of the outer medullary collecting duct. Sodium diffuses passively from the tubular fluid into the cell by a Na⁺ channel and then is extruded actively across the basolateral border by the Na⁺ pump (Na⁺-K⁺-ATPase). The same cells also contain a K⁺ channel at the luminal border, and this provides for K⁺ secretion across the luminal border into the tubular fluid. K⁺ enters the cell across the basolateral membrane via the Na⁺ pump, which maintains high intracellular K⁺ concentrations, and then exits the cell either via the luminal membrane K⁺ channel, giving rise to K⁺ secretion, or via a basolateral membrane K⁺ channel, recycling back into the interstitium. K⁺ secretion by these segments is the primary determinant of K⁺ excretion in the urine and hence provides regulation of K⁺ balance (see Figure 23-2).

The *mineralocorticoid hormone aldosterone* regulates both Na⁺ and K⁺ balance. Aldosterone secretion is stimulated by volume depletion (through the renin-angiotensin-aldosterone system), as is observed in hemorrhage and after the administration of high-ceiling loop diuretics. Aldosterone primarily acts in the *connecting tubule* and principal cells of the cortical collecting duct to *increase the reabsorption of Na⁺ and Cl⁻ and the secretion of K⁺*. Aldosterone acts by diffusing into the cell and binding to a cytosolic receptor. The receptor–hormone complex migrates into the nucleus, where it binds to specific sites on chromatin, which in turn induces RNA transcription and the

![Figure 23-2. Principal cells of the cortical collecting duct. Na⁺ and K⁺ are actively pumped at the basolateral border by the Na⁺ pump (Na⁺-K⁺-ATPase).](image)
synthesis (translation) of a myriad of new proteins called aldosterone-induced proteins (AIPs). These proteins include new luminal membrane Na\(^+\) channels and new Na\(^+\) pumps (Na\(^+\)-K\(^+\)-ATPase) at the basolateral membrane. In addition, aldosterone acts by increasing the opening of existing luminal membrane Na\(^+\) and K\(^+\) channels. These effects require protein synthesis, and so the effects on transport are apparent only after a delay of 1 or 2 hours. Na\(^+\) reabsorption in these cells is stimulated by enhanced Na\(^+\) entry and Na\(^+\) efflux after the increased opening of existing Na\(^+\) channels, by synthesis of new Na\(^+\) channels, and by synthesis of new Na\(^+\) pumps. The stimulation of net Na\(^+\) reabsorption causes a hyperpolarization of the tubule, with an increased luminal negativity (basolateral side positivity), and depolarization of the luminal membrane per se. This leads to a more favorable gradient for K\(^+\) to diffuse from the cell into the luminal fluid by K\(^+\) channels in the luminal cell membrane of the principal cells. Increased K\(^+\) diffusion (secretion) into the lumen, coupled with increased K\(^+\) uptake into the cell caused by the stimulation of the Na\(^+\) pump (increased Na\(^+\) efflux, increased K\(^+\) uptake) at the basolateral membrane, leads to an enhanced rate of K\(^+\) secretion into the tubular lumen. If the tubular flow rate does not change, the tubular fluid K\(^+\) concentration will be elevated, ultimately reducing the electrochemical gradient for K\(^+\) diffusion across the luminal membrane, limiting the rate of K\(^+\) secretion.

Conversely, under conditions in which the tubular flow rate to the collecting ducts is elevated, such as after treatment with a loop diuretic, the K\(^+\) concentration in the tubular fluid will be lower, providing a more favorable electrochemical gradient for K\(^+\) diffusion into the lumen, thereby leading to enhanced K\(^+\) secretion and in turn enhanced K\(^+\) excretion. This increased rate of flow-induced K\(^+\) secretion can lead to hypokalemia. This can be ameliorated by treatment with potassium supplements or administration of K\(^+\)-sparing diuretics such as amiloride and spironolactone. Amiloride acts to block the luminal Na\(^+\) channel in the late distal tubule and cortical collecting ducts, thereby markedly reducing Na\(^+\) reabsorption and in turn K\(^+\) secretion. Spironolactone, in contrast, competes with aldosterone for its receptor and depresses both Na\(^+\) reabsorption and K\(^+\) secretion in the late distal tubule and collecting duct.

**COMPREHENSION QUESTIONS**

[23.1] A hypertensive patient was prescribed the diuretic Lasix (furosemide) to increase urinary output. Furosemide, a “high-ceiling” diuretic, is a potent agent because it binds to and inhibits which of the following transport processes?

A. The Na\(^+\)-glucose cotransporter in the proximal tubule
B. The Na\(^+\)-K\(^+\) exchange pump in all nephron segments
C. The Na\(^+\)-K\(^+\)-Cl\(^-\) cotransporter in the thick ascending limb
D. The Na\(^+\)-Cl\(^-\) cotransporter in the distal convoluted tubule
E. The Na\(^+\) channel in the cortical collecting duct
A hypertensive patient is prescribed a loop diuretic such as Lasix without any supplements. One week later, the patient returns to the clinic complaining of dizziness, weakness, and nausea. The most likely cause of the patient’s worsening condition is the development of which of the following?

A. Metabolic acidosis
B. Hyponatremia
C. Hypercalcemia
D. Hypokalemia
E. Hypovolemia

A 35-year-old female is noted to have new-onset hypertension that is thought to be due to an aldosterone-secreting adrenal tumor. Which of the following is likely to be seen in this patient?

A. Hypertension markedly improved with furosemide
B. Elevated serum sodium level
C. Elevated serum potassium level
D. Elevated urinary cortisol level

C. Furosemide inhibits the Na⁺-K⁺-Cl⁻ cotransporter in the thick ascending limb. This is a critical transporter for reabsorption of NaCl from the thick ascending limb into the medullary interstitium. This transport of NaCl is the driving force behind the establishment of the hypertonicity of the medullary interstitium that is essential for the reabsorption of water from the collecting ducts and the generation of a concentrated urine. Inhibition of the thick ascending limb cotransporter will lead to both a greater load of NaCl left behind in the tubular fluid, increasing urinary NaCl levels, and a reduced hypertonicity of the medullary interstitium (less NaCl), decreasing the gradient for water reabsorption from the collecting ducts. This leads to a rapid and sustained increase in urinary volume flow along with significant urinary levels of NaCl. Hence, furosemide is a potent diuretic.

D. Loop diuretics such as Lasix (furosemide) potently inhibit the Na⁺-K⁺-Cl⁻ cotransporter in the thick ascending limb. NaCl reabsorption in the thick ascending limb through this cotransporter is the driving force behind the operation of the countercurrent multiplier and the ability to excrete a concentrated urine (and a diluted urine). Inhibition of this cotransporter leads to a much greater load of Na⁺ being delivered to the distal tubule and collecting ducts. With the increased delivery of Na⁺ and fluid to the late distal tubule and cortical collecting ducts, K⁺ secretion by the late distal tubule and cortical collecting ducts will be enhanced, leading to hypokalemia.
B. Aldosterone-secreting tumors may lead to hypertension, usually causing elevated serum sodium levels and low potassium levels (because of urinary reabsorption of sodium and excretion of potassium). One of the basic tests in the workup of newly diagnosed hypertension is serum electrolytes to assess for this disorder.

**PHYSIOLOGY PEARLS**

- Reabsorption of NaCl by the thick ascending limb underlies the generation of a medullary interstitial hypertonicity necessary for the passive reabsorption of water from the medullary collecting ducts.
- Loop diuretics are potent diuretics that inhibit the Na⁺-K⁺-Cl⁻ cotransporter at the luminal membrane of the thick ascending limb, thereby inhibiting NaCl reabsorption by this segment and water reabsorption by the medullary collecting ducts. They often are called high-ceiling diuretics.
- Administration of loop diuretics or other “upstream” diuretics can lead to increased tubular fluid flow to the late distal tubule and collecting ducts which, in turn, may stimulate K⁺ secretion and the development of hypokalemia.
- Potassium-sparing diuretics such as amiloride and spironolactone inhibit Na⁺ reabsorption and, in turn, K⁺ secretion by the late distal tubule and collecting ducts.
- Aldosterone induces the synthesis of a myriad of new proteins in the late distal tubule and cortical collecting duct, including the synthesis of new Na⁺ channels and Na⁺ pumps.

**REFERENCES**
