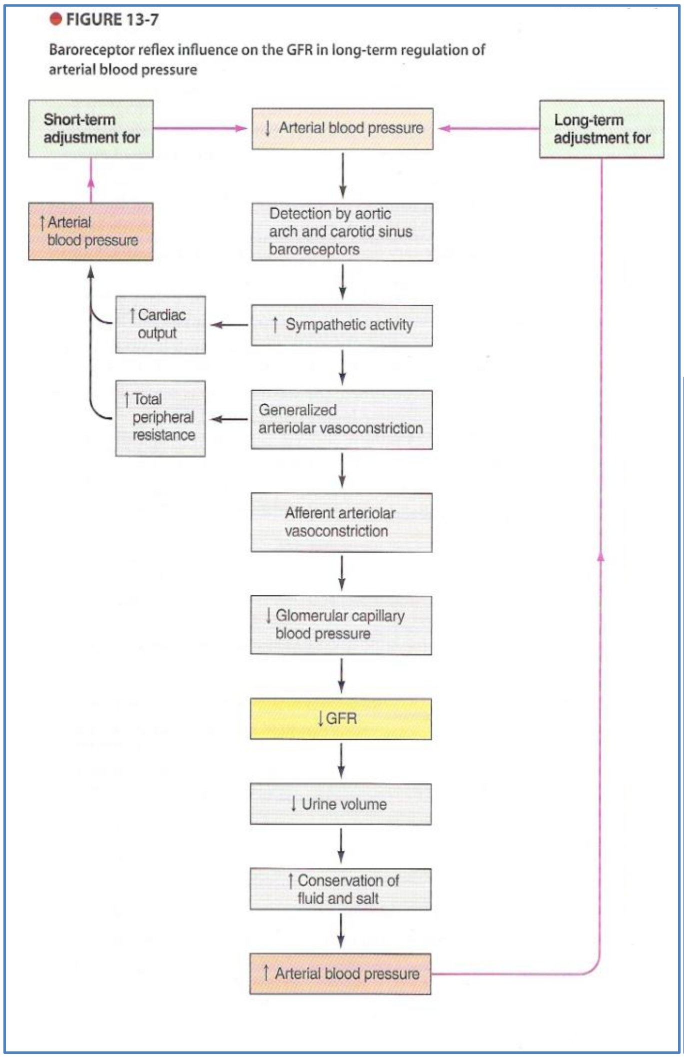
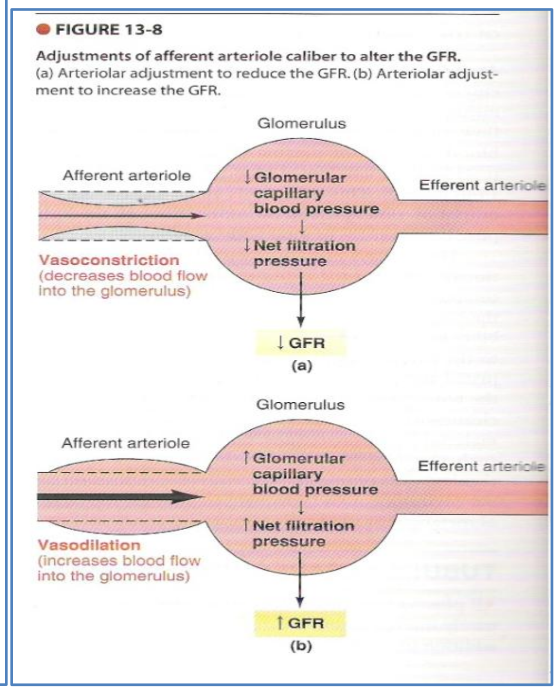




Tubular reabsorption is tremendous, highly selective, and variable

Tubular reabsorption is a highly selective process. All constituents except plasma proteins are at the same concentration in the glomerular filtrate as in plasma. In most cases, the quantity of each material that is reabsorbed is the amount required to maintain the proper composition and volume of the internal fluid environment. In general, the tubules have a high reabsorptive capacity for substances needed by the body and little or no reabsorptive capacity for substances of no value (Table 13-2). Accordingly, only a small percentage, if any, of filtered plasma constituents that are useful to the body are present in the urine, most having been reabsorbed and returned to the blood. Only excess amounts of essential materials such as electrolytes are excreted in the urine. For the essential plasma constituents regulated by the kidneys, absorptive capacity may vary depending on the body's needs. In contrast, a large percentage of filtered waste products is present in the urine. These wastes, which are useless or even potentially harmful to the body if allowed to accumulate, are not reabsorbed to any extent. Instead, they stay in the tubules to be eliminated in the urine. As H_2O and other valuable constituents are reabsorbed, the waste products remaining in the tubular fluid become highly concentrated.

Of the 125 ml/min filtered, typically 124 ml/min are reabsorbed. Considering the magnitude of glomerular filtration, the extent of tubular reabsorption is tremendous: The tubules typically reabsorb 99% of the filtered H_2O, 100% of the filtered sugar (2.5 pounds/day), and 99.5% of the filtered salt.

TABLE 13-2

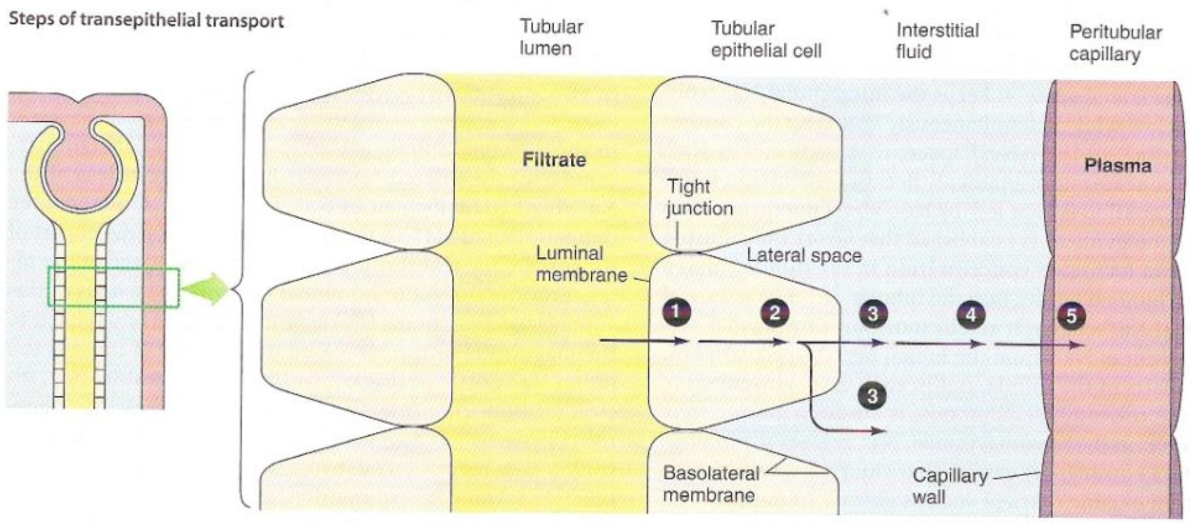
Fate of Various Substances Filtered by the Kidneys

SUBSTANCE	AVERAGE PERCENTAGE OF FILTERED SUBSTANCE REABSORBED	AVERAGE PERCENTAGE OF FILTERED SUBSTANCE EXCRETED
Water	99	1
Sodium	99.5	0.5
Glucose	100	0
Urea (a waste product)	50	50
Phenol (a waste product)	0	100

Tubular reabsorption involves transepithelial transport

FIGURE 13-9

Steps of transepithelial transport



To be reabsorbed (move from the filtrate to the plasma), a substance must traverse five distinct barriers:

1. the luminal cell membrane
2. the cytosol
3. the basolateral cell membrane
4. the interstital fluid
5. the capillary wall

Throughout its entire length, the tubule wall is one cell thick and is in close proximity to a surrounding peritubular capillary (Figure 13-9). Adjacent tubular cells do not come into contact with each other except where they are joined by tight junctions at their lateral edges near their *luminal membranes,* which face the tubular lumen. Interstitial fluid lies in the gaps between adjacent cells -the lateral spaces as well as between the tubules and capillaries. The *basolateral membrane* faces the interstitial fluid at the base and lateral edges of the cell. The tight junctions largely prevent substances from moving *between* the cells, so materials must pass *through* the cells to leave the tubular lumen and gain entry to the blood.

STEPS OF TRANSEPITHELIAL TRANSPORT

To be reabsorbed, a substance must traverse five distinct barriers **(**Figure 13-9):

- *Step* 1: It must leave the tubular fluid by crossing the luminal membrane of the tubular cell.
- *Step* 2: It must pass through the cytosol from one side of the tubular cell to the other.
- *Step* 3 It must traverse the basolateral membrane of the tubular cell to enter the interstitial fluid.
- *Step* 4: It must diffuse through the interstitial fluid.
- *Step* 5: It must penetrate the capillary wall to enter the blood plasma.

This entire sequence of steps is known as transepithelial ("across the epithelium") transport.

PASSIVE VERSUS ACTIVE REABSORPTION

The two types of tubular reabsorption-passive *reabsorption* and *active reabsorption-depend* on whether local energy expenditure is needed for reabsorbing a particular substance. In passive reabsorption, all steps in the transepithelial transport of a substance from the tubular lumen to the plasma are passive; that is, no energy is spent for the substance's net movement, which occurs down electrochemical or osmotic gradients. In contrast, active reabsorption takes place if anyone of the steps in the transepithelial transport of a substance requires energy, even if the four other steps are passive. With active reabsorption, net movement of the substance from the tubular lumen to the plasma occurs *against* an electrochemical gradient. Substances that are actively reabsorbed are of particular importance to the body, such as glucose, amino acids, and other organic nutrients, as well as Na^+ and other electrolytes such as PO_4^-.

An active Na^+ -K^+ ATPase pump in the basolateral membrane is essential for Na^+ reabsorption.

Sodium reabsorption is unique and complex. Of the total energy requirement of the kidneys, 80% is used for Na^+ transport, indicating the importance of this process. Unlike most filtered solutes, Na^+ is reabsorbed throughout most of the tubule, but to varying extents in different regions. Of the Na+ filtered, 99.5% is normally reabsorbed. Of the Na^+ reabsorbed, on average 67% is reabsorbed in the proximal tubule, 25% in the loop of Henle, and 8% in the distal and collecting tubules. Sodium reabsorption plays different important roles in each of these segments, as will become apparent as our discussion continues. Here is a preview of these roles.

Sodium reabsorption in the *proximal tubule* plays an essential role in reabsorbing glucose, amino acids, H_2O, Cl^-, and urea. Sodium reabsorption in the ascending limb of the loop *of Henle,* along with Sodium reabsorption in the *proximal tubule* plays a pivotal role in reabsorbing glucose, amino acids, H_2O, Cl^-, and urea.

Sodium reabsorption in the ascending limb of the loop *of Henle,* along with Cl^- reabsorption, plays a critical role in the kidneys' ability to produce urine of varying concentrations and volumes, depending on the body's need to conserve or eliminate H_2O. Sodium reabsorption in the *distal and collecting tubules* is variable and subject to hormonal control. It plays a key role in regulating ECF volume, which is important in long-term control of arterial blood pressure, and is also linked in part to K^+ secretion and H^+ secretion.

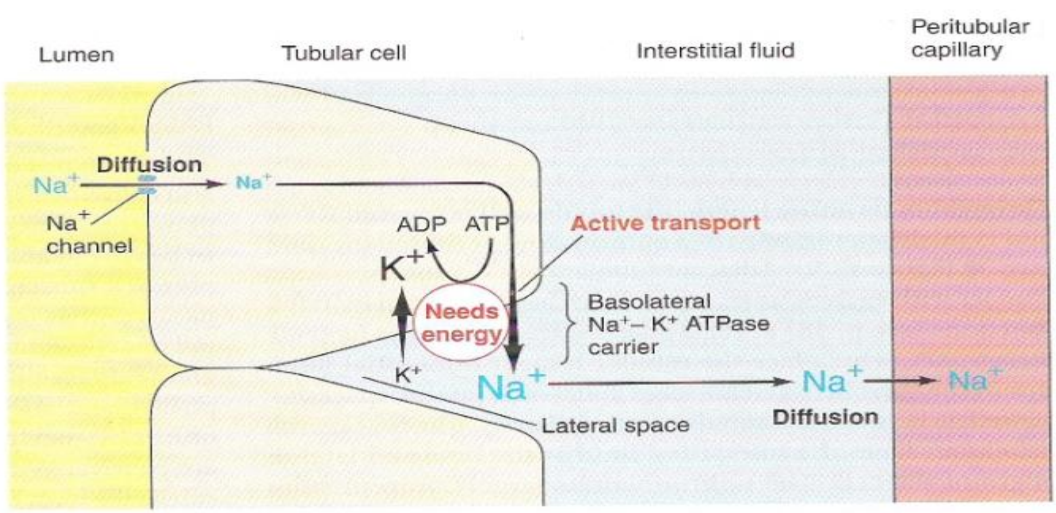


FIGURE 13-10

Sodium reabsorption. The basolateral Na^+–K^+ ATPase carrier actively transports Na^+ from the tubular cell into the interstitial fluid within the lateral space. This process establishes a concentration gradient for diffusion of Na^+ from the lumen into the tubular cell and from the lateral space into the peritubular capillary, accomplishing net transport of Na^+ from the tubular lumen into the blood at the expense of energy.

Sodium is reabsorbed throughout the tubule with the exception of the descending limb of the loop of Henle. You will learn about the significance of this exception later. Throughout all Na^+ -reabsorbing segments of the tubule, the active step in Na^+ reabsorption involves the energy-dependent Na^+-K^+ ATPase carrier located in the tubular cells basolateral membrane (Figure 13-10). This carrier is the same one that is in all cells and actively extrudes Na + from the cell. As this basolateral pump transports Na^+ out of the tubular cell into the lateral space, it keeps the intracellular Na^+ concentration low while it simultaneously builds up the concentration of Na^+ in the lateral space; that is, it moves Na^+ against a concentration gradient. Because the intracellular Na^+ concentration is kept low by basolateral pump activity, a concentration gradient is established that favors the diffusion of Na^+ from its higher concentration in the tubular lumen across the luminal border into the tubular cell. The nature of the luminal Na^+ channels and/or transport carriers that permit movement of Na^+ from the lumen into the cell varies for different parts of the tubule, but in each case, movement of Na^+ across the luminal membrane is always a passive step. For example, in the proximal tubule, Na^+ crosses the luminal border by a cotransport carrier that simultaneously moves Na^+ and an organic nutrient such as glucose from the lumen into the cell. You will learn more about this cotransport process shortly. By contrast, in the collecting duct, Na^+ crosses the luminal border through a Na^+ channel. Once Na^+ enters the cell across the luminal border by whatever means, it is actively extruded to the lateral space by the basolateral Na^+-K^+ pump. This step is the same throughout the tubule. Sodium continues to diffuse down a concentration gradient from its high concentration in the lateral space into the surrounding interstitial fluid and finally into the peritubular capillary blood. Thus net transport of Na^+ from the tubular lumen into the blood occurs at the expense of energy.

Aldosterone stimulates Na^+ reabsorption in the distal and collecting tubules

In the proximal tubule and loop of Henle, a constant percentage of the filtered Na^+ is reabsorbed regardless of the Na^+ load *(total amount* of Na^+ in the body fluids, *not the concentration* of Na^+ in the body fluids). In the distal part of the tubule, the reabsorption of a small percentage of the filtered Na^+ is subject to hormonal control. The extent of this controlled, discretionary reabsorption is inversely related to the magnitude of the Na^+ load in the body. If there is too much Na^+, little of this controlled Na^+ is reabsorbed; instead, it is lost in urine, thereby removing excess Na^+ from the body. If Na^+ is depleted, however, most or all of this controlled Na^+ is reabsorbed, conserving for the body Na^+ that otherwise would be lost in urine.

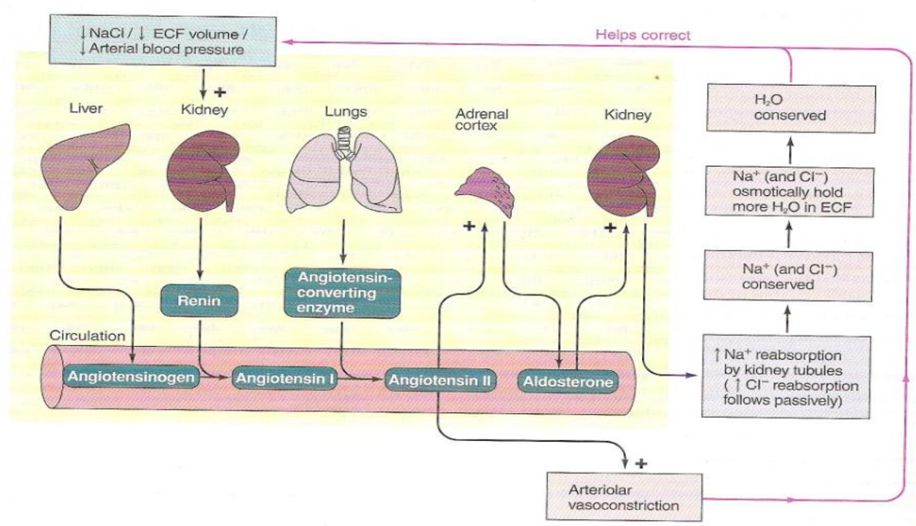
The Na^+ load in the body is reflected by the ECF volume. Sodium and its accompanying anion Cl^- account for more than 90% of the ECF's osmotic activity. (NaCl is common table salt.) Recall that osmotic pressure can be thought of loosely as a force that attracts and holds H_2O. When the Na^+ load is above normal and the ECF's osmotic activity is therefore increased, the extra Na^+ holds extra H_2O, expanding the ECF volume. Conversely, when the Na^+ load is below normal, thereby decreasing ECF osmotic activity, less H_2O than normal can be held in the ECF, so the ECF volume is reduced. Because plasma is part of the ECF, the most important result of a change in ECF volume is the matching change in blood pressure with expansion (↑blood pressure) or reduction (↓ blood pressure) of the plasma volume. Thus long-term control of arterial blood pressure ultimately depends on Na^+-regulating mechanisms.

ACTIVATION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The most important and best known hormonal system involved in regulating Na^+ is the **renin-angiotensin-aldosterone system** (RAAS). The juxtaglomerular apparatus (Figure 13-2) secretes a hormone, renin, into the blood in response to a fall in NaCl/ECF volume/blood pressure. These interrelated signals for increased renin secretion all indicate the need to expand the plasma volume to increase the arterial pressure to normal on a long-term basis. Through a complex series of events, increased renin secretion brings about increased Na^+ reabsorption by the distal and collecting tubules. Chloride always passively follows Na^+ down the electrical gradient established by sodium's active movement. The ultimate benefit of this salt retention is that it osrnoticallv promotes H_2O retention, which helps restore the plasma volume, thus being important in the long-term control of blood pressure.

FIGURE 13-11

Renin-angiotensin-aldosterone system. The kidneys secrete the hormone renin in response to reduced NaCl, ECF volume, and arterial blood pressure. Renin activates angiotensinogen, a plasma protein produced by the liver, into angiotensin I. Angiotensin I is converted into angiotensin II by angiotensin-converting enzyme (ACE) produced in the lungs. Angiotensin II stimulates the adrenal cortex to secrete the hormone aldosterone, which stimulates Na^+ reabsorption by the kidneys. The resulting retention of Na^+ exerts an osmotic effect that holds more H_2O in the ECF. Together, the conserved Na^+ and H_2O help correct the original stimuli that activated this hormonal system. Angiotensin II also promotes arteriolar vasoconstriction to help rectify the original stimuli.



Let's examine in further detail the RAAS mechanism by which renin secretion ultimately leads to increased Na^+ reabsorption (Figure 13-11). Once secreted into the blood, renin acts as an enzyme to activate angiotensinogen into angiotensin I. Angiotensinogen is a plasma protein synthesized by the liver and always present in the plasma in high concentration. On passing through the lungs via the pulmonary circulation, angiotensin I is converted into angiotensin II by angiotensin-converting enzyme (ACE), which is abundant in the pulmonary capillaries. Angiotensin II is the main stimulus for secretion of the hormone *aldosterone* from the adrenal cortex.

FUNCTIONS OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Among its actions, aldosterone increases Na + reabsorption by the distal and collecting tubules. It does so by promoting the insertion of additional Na^+ channels into the luminal membranes and additional Na^+-K^+ ATPase carriers into the basolateral membranes of the distal and collecting tubular cells. The net result is a greater passive inward flux of Na^+ into the tubular cells from the lumen and increased active pumping of Na^+ out of the cells into the plasma-that is, an increase in Na^+ reabsorption, with Cl^- following passively. RAAS thus promotes salt retention and a resulting H_2O retention and rise in arterial blood pressure.

In addition to stimulating aldosterone secretion, angiotensin II is also a potent constrictor of the systemic arterioles, directly increasing blood pressure by increasing total peripheral resistance. The opposite situation exists when the Na^+ load, ECF and plasma volume, and arterial blood pressure are above normal. Under these circumstances, renin secretion is inhibited. Therefore, because angiotensinogen is not activated to angiotensin I and II, aldosterone secretion is not stimulated. Without aldosterone, the small aldosterone-dependent part of Na^+ reabsorption in the distal segments of the tubule does not occur. Instead, this nonreabsorbed Na^+ is lost in urine. In the absence of aldosterone, the ongoing loss of this small percentage of filtered Na^+ can rapidly remove excess Na^+ from the body. Even though only about 8% of the filtered Na^+ depends on aldosterone for reabsorption, this small loss, multiplied many times as the entire plasma volume is filtered through the kidneys many times per day, can lead to a sizable loss of Na^+.

Many diuretics, therapeutic agents that cause d*iuresis* (increased urinary output) and thus promote loss of fluid from the body, function by inhibiting tubular reabsorption of Na^+ As more Na^+ is excreted, more H_2O is also lost from the body, helping remove the excess ECF. Diuretics are often beneficial in treating congestive heart failure as well as certain cases of hypertension. ACE inhibitor drugs, which block the action of angiotensin-converting enzyme (ACE), are also beneficial in treating these conditions.

Atrial natriuretic peptide inhibits Na^+ reabsorption

Whereas RAAS exerts the most powerful influence on the renal handling of Na^+, this Na^+ -retaining, blood pressure-raising system is opposed by a Na^+-losing, blood pressure-lowering system that involves the hormone atrial natriuretic peptide (ANP) *(natriuretic* means "inducing excretion of large amounts of sodium in the urine"). The heart, in addition to its pump action, produces ANP, which is stored in specialized cardiac atrial muscle cells and is released from the atria when the heart is mechanically stretched by expansion of the ECF volume, including the circulating plasma volume. This expansion, which occurs as a result of Na^+ and H_2O retention, increases arterial blood pressure. In turn, the main action of ANP is to inhibit Na^+ reabsorption in the distal parts of the nephron, thus increasing Na^+ excretion in the urine. This natriuresis brings about an 'accompanying diuresis. As a result, more salt and water are excreted in the urine. Besides indirectly lowering blood pressure by reducing the Na^+ load and hence the fluid load in the body; ANP also directly lowers blood pressure by decreasing the cardiac output and reducing peripheral vascular resistance by inhibiting sympathetic nervous activity to the heart and blood vessels.

Glucose and amino acids are reabsorbed by Na + -dependent secondary active transport

Large quantities of nutritionally important organic molecules such as glucose and amino acids are filtered each day. Because these substances normally are completely reabsorbed back into the blood by energy- and Na^+ -dependent mechanisms located in the proximal tubule, none of these materials are usually excreted in the urine. This rapid and thorough reabsorption early in the tubules protects against the loss of these important organic nutrients.

Glucose and amino acids are transferred by secondary active transport. With this process, specialized *cotransport carriers* located in the proximal tubule simultaneously transfer both Na + and the specific organic molecule from the lumen into the cell. This luminal cotransport carrier is the means by which Na^+ passively crosses the luminal membrane in the proximal tubule. The lumen-to-cell Na^+ concentration gradient maintained by the energy-consuming basolateral Na^+-K^+ pump drives this cotransport system and pulls the organic molecule against its concentration gradient without the direct expenditure of energy. Specifically, the Na^+ gradient, not ATP, is directly responsible for the cotransport carrier picking up its passengers from the lumen, changing shape, and dropping them off inside the cell. The movement of Na+ into the cell by this cotransport carrier is downhill because the intracellular Na^+ concentration is low (due to the Na^+-K^+ pump), but the movement of glucose (or amino acid) is uphill because glucose becomes concentrated in the cell. Because the overall process of glucose and amino acid reabsorption depends on the use of energy, these organic molecules are considered to be actively reabsorbed, even though energy is not used directly to transport them across the membrane. In essence, glucose and amino acids get a "free ride" at the expense of energy already used in the reabsorption of Na^+. Once transported into the tubular cells, glucose and amino acids passively diffuse down their concentration gradients across the basolateral membrane into the plasma, facilitated by a carrier that is not dependent on energy.

In general, actively reabsorbed substances exhibit a tubular maximum

All actively reabsorbed substances bind with plasma membrane carriers that transfer them across the membrane against a concentration gradient. Each carrier is specific for the types of substances it can transport; for example, the glucose cotransport carrier cannot transport amino acids, or vice versa. Because a limited number of each carrier type are present in the cells lining the tubules, there is an upper limit on how much of a particular substance that can be actively transported from the tubular fluid in a given period of time. The maximum reabsorption rate is reached when all the carriers specific for a particular substance are fully occupied or saturated, so they cannot handle any additional passengers at that time. This transport maximum is designated as the tubular maximum, or T_m. Any quantity of a substance filtered beyond its T_m is not reabsorbed, and escapes instead into the urine. With the exception of Na^+, all actively reabsorbed substances have a tubular maximum.

Glucose is an example of an actively reabsorbed substance that is not regulated by the kidneys

The normal plasma concentration of glucose is 100 mg of glucose/100 ml of plasma. Because glucose is freely filterable at the glomerulus, it passes into Bowman's capsule at the same concentration it has in the plasma. Accordingly, 100 mg of glucose are present in every 100 ml of plasma filtered. With 125 ml of plasma normally being filtered each minute (average GFR = 125 ml/min), 125 mg of glucose pass into Bowman's capsule with this filtrate every minute. The quantity of any substance filtered per minute, known as its filtered load, can be calculated as follows:

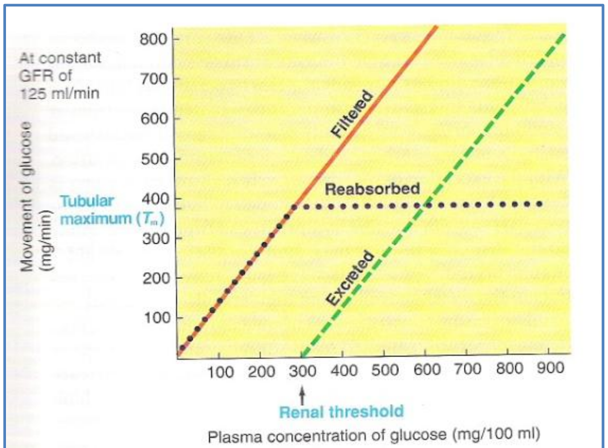


FIGURE 13-12

Renal handling of glucose as a function of plasma glucose concentration. At a constant GFR, the quantity of glucose filtered per minute is directly proportional to the plasma concentration of glucose. All the filtered glucose can be reabsorbed up to the tubular maximum (T_m). If the amount of glucose filtered per minute exceeds the T_m, the maximum amount of glucose is reabsorbed (a T_m worth), and the rest stays in the filtrate to be excreted in urine. The renal threshold is the plasma concentration at which the T_m is reached and glucose first starts appearing in the urine.

Filtered load of a substance = plasma concentration of the substance X GFR

Filtered load of glucose = 100 mg/100 ml X 125 ml/min
= 125 mg/min

At a constant GFR, the filtered load of glucose is directly proportional to the plasma glucose concentration. Doubling the plasma glucose concentration to 200 mg/100 ml doubles the filtered load of glucose to 250 mg/min, and so on **(**Figure 13-12).

TUBULAR MAXIMUM FOR GLUCOSE

The T_m for glucose averages 375 mg/min; that is, the glucose carrier mechanism is capable of actively reabsorbing up to 375 mg of glucose per minute before it reaches its maximum transport capacity. At a normal plasma glucose concentration of 100 mg/100 ml, the 125 mg of glucose filtered per minute can readily be reabsorbed by the glucose carrier mechanism, because the filtered load is well below the T_m for glucose. Ordinarily, therefore, no glucose appears in the urine. Not until the filtered load of glucose exceeds 375 mg/min is the T_m reached. When more glucose is filtered per minute than can be reabsorbed because the T_m is exceeded, the maximum amount is reabsorbed, while the rest stays in the filtrate to be excreted. Accordingly, the plasma glucose concentration must be greater than 300 mg/100 ml-more than three times the normal value-before glucose starts spilling into the urine.

RENAL THRESHOLD FOR GLUCOSE

The plasma concentration at which the T_m of a particular substance is reached and the substance first starts appearing in urine is called the renal threshold. At the average T_m of 375 mg/min and GFR of 125 ml/min, the renal threshold for glucose is 300 mg/100 ml.

The plasma glucose concentration can become extremely high in *diabetes mellitus*, an endocrine disorder involving inadequate insulin action. Insulin is a pancreatic hormone that facilitates transport of glucose into many body cells. When cellular glucose uptake is impaired, glucose that cannot gain entry into cells stays in the plasma, elevating the plasma glucose concentration. Consequently, although glucose does not normally appear in urine, it is found in the urine of people with diabetes when the plasma glucose concentration exceeds the renal threshold, even though renal function has not changed.

REASON WHYTHE KIDNEYS DO NOT REGULATE GLUCOSE

The kidneys do not influence plasma glucose concentration over a wide range of values from abnormally low levels up to three times the normal level. Because the T_m for glucose is well above the normal filtered load, the kidneys usually conserve all the glucose, thereby protecting against loss of this important nutrient in urine. The kidneys do not regulate glucose, because they do not maintain glucose at some specific plasma concentration. Instead, this concentration is normally regulated by endocrine and liver mechanisms, with the kidneys merely maintaining whatever plasma glucose concentration is set by these other mechanisms.

Phosphate is an example of an actively reabsorbed substance that is regulated by the kidneys

The kidneys do directly contribute to the regulation of many electrolytes, such as phosphate (PO_4^-) and calcium (Ca^{2+}), because the renal thresholds of these inorganic ions equal their normal plasma concentrations. Unlike the reabsorption of organic nutrients, the reabsorption of PO_4^- and Ca^{2+} is also subject to hormonal control. Parathyroid hormone can alter the renal thresholds for PO_4^- and Ca^{2+}, thus adjusting the quantity of these electrolytes conserved, depending on the body's momentary needs.

Active Na^+ reabsorption is responsible for the passive reabsorption of $C1^-$, H_2O, and urea.

Not only is secondary active reabsorption of glucose and amino acids linked to the basolateral Na^+-K^+ pump, but passive reabsorption of Cl^- , H_2O, and urea also depends on this active Na^+ reabsorption mechanism.

CHLORIDE REABSORPTION

The negatively charged chloride ions are passively reabsorbed down the electrical gradient created by the active reabsorption of the positively charged sodium ions. The amount of Cl^- reabsorbed is determined by the rate of active Na^+ reabsorption, instead of being directly controlled by the kidneys.

WATER REABSORPTION

Water is passively reabsorbed throughout the length of the tubule as H_2O osmotically follows Na^+ that is actively reabsorbed. Of the H_2O filtered, 65%-117 liters per day-is passively reabsorbed by the end of the proximal tubule. Neither the proximal tubule nor indeed any other part of the tubule directly requires energy for this tremendous reabsorption of H_2O. Another 15% of the filtered H_20 is obligatorily reabsorbed from the loop of Henle. This 80% of the filtered H_2O is reabsorbed in the proximal tubule and Henle's loop regardless of the H_2O load in the body and is not subject to regulation. Variable amounts of the remaining 20% are reabsorbed in the distal portions of the tubule; the extent of reabsorption in the distal and collecting tubules is under direct hormonal control, depending on the body's state of hydration.

During reabsorption, H_2O passes through aquaporins, or water channels, formed by specific plasma membrane proteins in the tubular cells. Different types of water channels are present in various parts of the nephron. The water channels in the proximal tubule are always open, accounting for the high H_2O permeability of this region. The channels in the distal parts of the nephron, in contrast, are regulated by the hormone *vasopressin*, accounting for the variable H_2O reabsorption in this region.

UREA REABSORPTION

In addition to Cl^- and H_2O, passive reabsorption of urea is also indirectly linked to active Na^+ reabsorption. Urea is a waste product from the breakdown of protein. The osmotically induced reabsorption of H_2O in the proximal tubule secondary to active Na^+

reabsorption produces a concentration gradient for urea that favors passive reabsorption of this waste, as follows (Figure 13-13). Extensive reabsorption of H_2O in the proximal tubule gradually reduces the original 125 ml/min of filtrate until only 44 ml/min of fluid remain in the lumen by the end of the proximal tubule. As a result, the urea concentration within the tubular fluid becomes much greater than the urea concentration in the adjacent capillaries. Therefore, a concentration gradient is created for urea to passively diffuse from the tubular lumen into the peritubular capillary plasma. Because the walls of the proximal tubules are only somewhat permeable to urea, only about 50% of the filtered urea is passively reabsorbed by this means.

The urea concentration in the plasma becomes elevated only in impaired kidney function, when much less than half of the urea is removed. An elevated urea level was one of the first chemical characteristics to be identified in the plasma of patients with severe renal failure. Accordingly, clinical measurement of blood urea nitrogen (BUN) came into use as a crude assessment of kidney function.

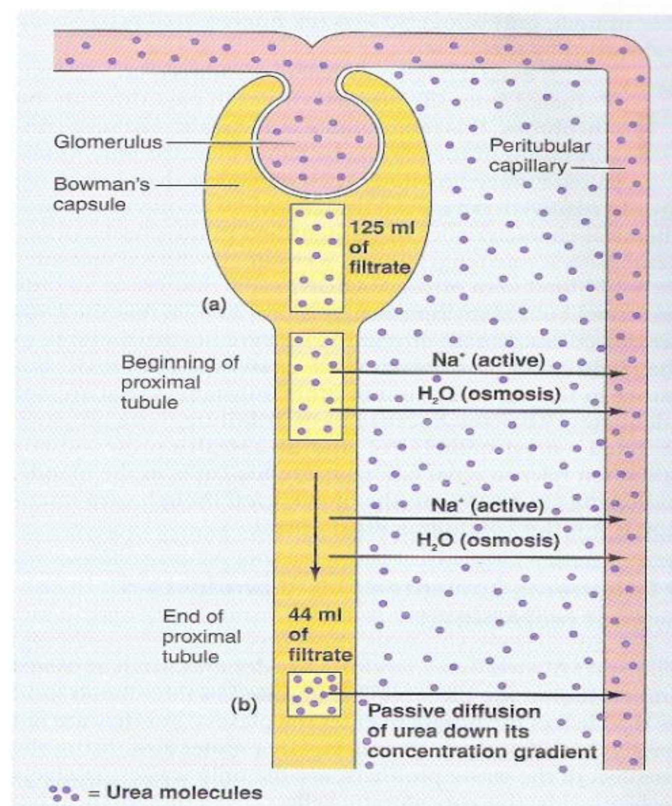


FIGURE 13-13

Passive reabsorption of urea at the end of the proximal tubule. (a) In Bowman's capsule and at the beginning of the proximal tubule, urea is at the same concentration as in the plasma and surrounding interstitial fluid. (b) By the end of the proximal tubule, 65% of the original filtrate has been reabsorbed, concentrating the filtered urea in the remaining filtrate. This establishes a concentration gradient favoring passive reabsorption of urea.

In general, unwanted waste products are not reabsorbed

The other filtered waste products besides urea, such as *phenol* and *creatinine*, are likewise concentrated in the tubular fluid as H_2O leaves the filtrate to enter the plasma, but they are not passively reabsorbed, as urea is. Urea molecules, being the smallest of the waste products, are the only wastes passively reabsorbed by this concentrating effect. Even though the other wastes are also concentrated in the tubular fluid, they cannot leave the lumen down their concentration gradients to be passively reabsorbed, because they cannot permeate the tubular wall. Therefore, the waste products, not being reabsorbed, generally remain in the tubules and are excreted in the urine in highly concentrated form.