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**MEDICINE AND SURGERY**

**300LV**

**RENAL PHYSIOLOGY, BODY FLUID AND TEMPERATURE REGULATION**

1. ***Discuss the role of kidney in glucose homeostasis***

The kidneys synthesize glucose from amino acids and other precursors during prolonged fasting, a process referred to as *gluconeogenesis*. The kidneys’ capacity to add glucose to the blood during prolonged periods of fasting rivals that of the liver.

With chronic kidney disease or acute failure of the kidneys, these homeostatic functions are disrupted and severe abnormalities of body fluid volumes and composition rapidly occur. With complete renal failure, enough potassium, acids, fluid, and other substances accumulate in the body to cause death within a few days, unless clinical interventions such as hemodialysis are initiated to restore, at least partially, the body fluid and electrolyte balances.

Filtered load of glucose ■ increases in direct proportion to the plasma glucose concentration (filtered load of glucose = GFR × [P]glucose).

2. Reabsorption of glucose: a. Na+–glucose cotransport in the proximal tubule reabsorbs glucose from tubular fluid into the blood. There are a limited number of Na+–glucose carriers. b. At plasma glucose concentrations less than 250 mg/dL, all of the filtered glucose can be reabsorbed because plenty of carriers are available; in this range, the line for reabsorption is the same as that for filtration. c. At plasma glucose concentrations greater than 350 mg/dL, the carriers are saturated. Therefore, increases in plasma concentration above 350 mg/dL do not result in increased rates of reabsorption. The reabsorptive rate at which the carriers are saturated is the Tm.

3. Excretion of glucose: a. At plasma concentrations less than 250 mg/dL, all of the filtered glucose is reabsorbed and excretion is zero. Threshold(defined as the plasma concentration at which glucose first appears in the urine) is approximately 250 mg/dL. b. At plasma concentrations greater than 350 mg/dL, reabsorption is saturated (Tm). Therefore, as the plasma concentration increases, the additional filtered glucose cannot be reabsorbed and is excreted in the urine.

In the adult human, the transport maximum for glucose averages about 375 mg/min, whereas the filtered load of glucose is only about 125 mg/min (GFR × plasma glucose = 125 ml/min × 1 mg/ml). With large increases in GFR and/or plasma glucose concentration that

increase the filtered load of glucose above 375 mg/min, the excess glucose filtered is not reabsorbed and passes into the urine.

However, when the plasma concentration of glucose rises above about 200 mg/100 ml, increasing the filtered load to about 250 mg/min, a small amount of glucose begins to appear in the urine. This point is termed the threshold for glucose. Note that this appearance of glucose in the urine (at the threshold) occurs before the transport maximum is reached. One reason for the difference between threshold and transport maximum is that not all nephrons have the same transport maximum for glucose, and some of the nephrons therefore begin to excrete glucose before others have reached their transport maximum. The overall transport maximum for the kidneys, which is normally about 375 mg/min, is reached when all nephrons have reached their maximal capacity to reabsorb glucose. The plasma glucose of a healthy person almost never becomes high enough to cause glucose excretion in the urine, even after eating a meal. However, in uncontrolled diabetes mellitus, plasma glucose may rise to high levels, causing the filtered load of glucose to exceed the transport maximum and resulting in urinary glucose excretion.

1. ***Discuss the process of micturition***.

Micturition is the process by which the urinary bladder empties when it becomes filled. This process involves two main steps: First, the bladder fills progressively until the tension in its walls rises above a threshold level. This tension elicits the second step, which is a nervous reflex called the micturition reflex that empties the bladder or, if this fails, at least causes a conscious desire to urinate. Although the micturition reflex is an autonomic spinal cord reflex, it can also be inhibited or facilitated by centers in the cerebral cortex or brain stem. Urine that is expelled from the bladder has essentially the same composition as fluid flowing out of the collecting ducts; there are no significant changes in the composition of urine as it flows through the renal calyces and ureters to the bladder. Urine flowing from the collecting ducts into the renal calyces stretches the calyces and increases their inherent pacemaker activity, which in turn initiates peristaltic contractions that spread to the renal pelvis and then downward along the length of the ureter, thereby forcing urine from the renal pelvis toward the bladder. In adults, the ureters are normally 25 to 35 centimeters (10 to 14 inches) long. The walls of the ureters contain smooth muscle and are innervated by both sympathetic and parasympathetic nerves, as well as by an intramural plexus of neurons and nerve fibers that extends along the entire length of the ureters. As with other visceral smooth muscle, peristaltic contractions in the ureter are enhanced by parasympathetic stimulation and inhibited by sympathetic stimulation. The ureters enter the bladder through the detrusor muscle in the trigone region of the bladder. Normally, the ureters course obliquely for several centimeters through the bladder wall. The normal tone of the detrusor muscle in the bladder wall tends to compress the ureter, thereby preventing backflow (reflux) of urine from the bladder when pressure builds up in the bladder during micturition or bladder compression. Each peristaltic wave along the ureter increases the pressure within the ureter so that the region passing through the bladder wall opens and allows urine to flow into the bladder.

**MICTURITION REFLEX** As the bladder fills, many superimposed micturition contractions begin to appear. They are the result of a stretch reflex initiated by sensory stretch receptors in the bladder wall, especially by the receptors in the posterior urethra when this area begins to fill with urine at the higher bladder pressures. Sensory signals from the bladder stretch receptors are conducted to the sacral segments of the cord through the pelvic nerves and then reflexively back again to the bladder through the parasympathetic nerve fibers by way of these same nerves. When the bladder is only partially filled, these micturition contractions usually relax spontaneously after a fraction of a minute, the detrusor muscles stop contracting, and pressure falls back to the baseline. As the bladder continues to fill, the micturition reflexes become more frequent and cause greater contractions of the detrusor muscle. Once a micturition reflex begins, it is “self-regenerative.” That is, initial contraction of the bladder activates the stretch receptors to cause a greater increase in sensory impulses from the bladder and posterior urethra, which causes a further increase in reflex contraction of the bladder; thus, the cycle is repeated again and again until the bladder has reached a strong degree of contraction. Then, after a few seconds to more than a minute, the self regenerative reflex begins to fatigue and the regenerative cycle of the micturition reflex ceases, permitting the bladder to relax. Thus, the micturition reflex is a single complete cycle of (1) progressive and rapid increase of pressure, (2) a period of sustained pressure, and (3) return of the pressure to the basal tone of the bladder. Once a micturition reflex has occurred but has not succeeded in emptying the bladder, the nervous elements of this reflex usually remain in an inhibited state for a few minutes to 1 hour or more before another micturition reflex occurs. As the bladder becomes more and more filled, micturition reflexes occur more and more often and more and more powerfully. Once the micturition reflex becomes powerful enough, it causes another reflex, which passes through the pudendal nerves to the external sphincter to inhibit it. If this inhibition is more potent in the brain than the voluntary constrictor signals to the external sphincter, urination will occur. If not, urination will not occur until the bladder fills still further and the micturition reflex becomes more powerful.

1. ***Explain juxtaglomerular apparatus***

Juxtaglomerular apparatus is a specialized organ situated near the glomerulus of each nephron (juxta = near).

STRUCTURE OF JUXTAGLOMERULAR APPARATUS

Juxtaglomerular apparatus is formed by three different structures: 1. Macula densa 2. Extraglomerular mesangial cells 3. Juxtaglomerular cells.

**MACULA DENSA** Macula densa is the end portion of thick ascending segment before it opens into distal convoluted tubule. It is situated between afferent and efferent arterioles of the same nephron. It is very close to afferent arteriole. Macula densa is formed by tightly packed cuboidal epithelial cells.

**EXTRAGLOMERULAR MESANGIAL CELLS** Extraglomerular mesangial cells are situated in the triangular region bound by afferent arteriole, efferent arteriole and macula densa. These cells are also called agranular cells, lacis cells or Goormaghtigh cells.

*Glomerular Mesangial Cells,* besides extraglomerular mesangial cells there is another type of mesangial cells situated in between glomerular capillaries called glomerular mesangial or intraglomerular mesangial cells. Glomerular mesangial cells support the glomerular capillary loops by surrounding the capillaries in the form of a cellular network. These cells play an important role in regulating the glomerular filtration by their contractile property. Glomerular mesangial cells are phagocytic in nature. These cells also secrete glomerular interstitial matrix, prostaglandins and cytokines.

**JUXTAGLOMERULAR CELLS**. Juxtaglomerular cells are specialized smooth muscle cells situated in the wall of afferent arteriole just before it enters the Bowman capsule. These smooth muscle cells are mostly present in tunica media and tunica adventitia of the wall of the afferent arteriole. Juxtaglomerular cells are also called granular cells because of the presence of secretary granules in their cytoplasm.

Polar Cushion or Polkissen Juxtaglomerular cells form a thick cuff called polar cushion or polkissen around the afferent arteriole before it enters the Bowman capsule.

**FUNCTIONS OF JUXTAGLOMERULAR APPARATUS**

Primary function of juxtaglomerular apparatus is the secretion of hormones. It also regulates the glomerular blood flow and glomerular filtration rate.

 SECRETION OF HORMONES: Juxtaglomerular apparatus secretes two hormones: 1. Renin 2. Prostaglandin.

1. **Renin**: Juxtaglomerular cells secrete renin. Renin is a peptide with 340 amino acids. Along with angiotensins, renin forms the renin-angiotensin system, which is a hormone system that plays an important role in the maintenance of blood pressure.

Stimulants for renin secretion Secretion of renin is stimulated by four factors: i. Fall in arterial blood pressure ii. Reduction in the ECF volume iii. Increased sympathetic activity iv. Decreased load of sodium and chloride in macula densa.

1. **Prostaglandin**: Extraglomerular mesangial cells of juxtaglomerular apparatus secrete prostaglandin. Prostaglandin is also secreted by interstitial cells of medulla called type I medullary interstitial cells.

 *SECRETION OF OTHER SUBSTANCES*

1. Extraglomerular mesangial cells of juxtaglomerular apparatus secrete cytokines like interleukin-2 and tumor necrosis factor 2. Macula densa secretes thromboxane A2.

REGULATION OF GLOMERULAR BLOOD FLOW AND GLOMERULAR FILTRATION RATE

Macula densa of juxtaglomerular apparatus plays an important role in the feedback mechanism called tubuloglomerular feedback mechanism, which regulates the renal blood flow and glomerular filtration rate.

4. ***Discuss the role of kidney in regulation of blood pressure***

The sympathetic nervous system plays a major role in short-term arterial blood pressure regulation primarily through the effects of the nervous system on total peripheral vascular resistance and capacitance, as well as on cardiac pumping ability. The body, however, also has powerful mechanisms for regulating arterial pressure week after week and month after month. This long-term control of arterial pressure is closely intertwined with homeostasis of body fluid volume, which is determined by the balance between the fluid intake and output. For long-term survival, fluid intake and output must be precisely balanced, a task that is performed by multiple nervous and hormonal controls and by local control systems within the kidneys that regulate their excretion of salt and water. In this chapter we discuss these renal–body fluid systems that play a major role in long-term blood pressure regulation.

RENAL–BODY FLUID SYSTEM FOR ARTERIAL PRESSURE CONTROL The renal–body fluid system for arterial pressure control acts slowly but powerfully as follows: If blood volume increases and vascular capacitance is not altered, arterial pressure will also increase. The rising pressure, in turn, causes the kidneys to excrete the excess volume, thus returning the pressure back toward normal. In the phylogenetic history of animal development, this renal–body fluid system for pressure control is a primitive one. It is fully operative in one of the lowest of vertebrates, the hagfish. This animal has a low arterial pressure, only 8 to 14 mm Hg, and this pressure increases almost directly in proportion to its blood volume. The hagfish continually drinks sea water, which is absorbed into its blood, increasing the blood volume and blood pressure. However, when the pressure rises too high, the kidney simply excretes the excess volume into the urine and relieves the pressure. At low pressure, the kidney excretes less fluid than is ingested. Therefore, because the hagfish continues to drink, extracellular fluid volume, blood volume, and pressure all build up again to the higher levels. This primitive mechanism of pressure control has survived throughout the ages, almost as it functions in the hagfish; in humans, kidney output of water and salt is just as sensitive—if not more so—to pressure changes as in the hagfish. Indeed, an increase in arterial pressure in the human of only a few mm Hg can double renal output of water, a phenomenon called pressure diuresis, as well as double the output of salt, which is called pressure natriuresis.

**The Renal–Body Fluid Mechanism Provides Nearly Infinite Feedback Gain for Long-term Arterial**

**Pressure Control**.. Over a long period, the water and salt output must equal the intake. Now let us see what happens if the arterial pressure increases above or decreases below the equilibrium point. First, assume that the arterial pressure rises to 150 mm Hg. At this level, the renal output of water and salt is about three times as great as intake. Therefore, the body loses fluid, the blood volume decreases, and the arterial pressure decreases. Furthermore, this “negative balance” of fluid will not cease until the pressure falls all the way back exactly to the equilibrium level. Indeed, even when the arterial pressure is only a few mm Hg greater than the equilibrium level, there still is slightly more loss of water and salt than intake, so the pressure continues to fall that last few mm Hg until the pressure eventually returns exactly to the equilibrium point. If the arterial pressure falls below the equilibrium point, the intake of water and salt is greater than the output. Therefore, body fluid volume increases, blood volume increases, and the arterial pressure rises until once again it returns to the equilibrium point. This return of the arterial pressure always back to the equilibrium point is the near-infinite feedback gain principle for control of arterial pressure by the renal–body fluid mechanism.

volume-loading hypertension.

**THE RENIN-ANGIOTENSIN SYSTEM: ITS ROLE IN ARTERIAL PRESSURE CONTROL:** Aside from the capability of the kidneys to control arterial pressure through changes in extracellular fluid volume, the kidneys also have another powerful mechanism for controlling pressure: the renin-angiotensin system. Renin is a protein enzyme released by the kidneys when the arterial pressure falls too low. In turn, it raises the arterial pressure in several ways, thus helping to correct the initial fall in pressure.

COMPONENTS OF THE RENIN-ANGIOTENSIN SYSTEM

This shows the functional steps by which the renin-angiotensin system helps to regulate arterial pressure. Renin is synthesized and stored in an inactive form called prorenin in the juxtaglomerular cells (JG cells) of the kidneys. The JG cells are modified smooth muscle cells located mainly in the walls of the afferent arterioles immediately proximal to the glomeruli. When the arterial pressure falls, intrinsic reactions in the kidneys cause many of the prorenin molecules in the JG cells to split and release renin. Most of the renin enters the renal blood and then passes out of the kidneys to circulate throughout the entire body. However, small amounts of the renin do remain in the local fluids of the kidney and initiate several intrarenal functions. Renin itself is an enzyme, not a vasoactive substance. Renin acts enzymatically on another plasma protein, a globulin called renin substrate (or angiotensinogen), to release a 10-amino acid peptide, angiotensin I. Angiotensin I has mild vasoconstrictor properties but not enough to cause significant changes in circulatory function. The renin persists in the blood for 30 minutes to 1 hour and continues to cause formation of still more angiotensin I during this entire time. Within a few seconds to minutes after formation of angiotensin I, two additional amino acids are split from the angiotensin I to form the 8-amino acid peptide angiotensin II. This conversion occurs to a great extent in the lungs while the blood flows through the small vessels of the lungs, catalyzed by an enzyme called angiotensinconverting enzyme that is present in the endothelium of the lung vessels. Other tissues such as the kidneys and blood vessels also contain converting enzyme and therefore form angiotensin II locally. Angiotensin II is an extremely powerful vasoconstrictor, and it affects circulatory function in other ways as well. However, it persists in the blood only for 1 or 2 minutes because it is rapidly inactivated by multiple blood and tissue enzymes collectively called angiotensinases. Angiotensin II has two principal effects that can elevate arterial pressure. The first of these, vasoconstriction in many areas of the body, occurs rapidly. Vasoconstriction occurs intensely in the arterioles and much less so in the veins. Constriction of the arterioles increases the total peripheral resistance, thereby raising the arterial pressure, as demonstrated at the bottom of the schema in Figure 19-10. Also, the mild constriction of the veins promotes increased venous return of blood to the heart, thereby helping the heart pump against the increasing pressure. The second principal means by which angiotensin II increases the arterial pressure is to decrease excretion of both salt and water by the kidneys. This action slowly increases the extracellular fluid volume, which then increases the arterial pressure during subsequent hours and days. This long-term effect, acting through the extracellular fluid volume mechanism, is even more powerful than the acute vasoconstrictor mechanism in eventually raising the arterial pressure.

1. ***Discuss the role of kidney in calcium homeostasis***

Extracellular fluid calcium ion concentration normally remains tightly controlled within a few percentage points of its normal level, 2.4 mEq/L. When calcium ion concentration falls to low levels (hypocalcemia), the excitability of nerve and muscle cells increases markedly and can in extreme cases result in hypocalcemic tetany. This condition is characterized by spastic skeletal muscle contractions. Hypercalcemia (increased calcium concentration) depresses neuromuscular excitability and can lead to cardiac arrhythmias. About 50 percent of the total calcium in the plasma (5 mEq/L) exists in the ionized form, which is the form that has biological activity at cell membranes. The remainder is either bound to the plasma proteins (about 40 percent) or complexed in the non-ionized form with anions such as phosphate and citrate (about 10 percent). Changes in plasma hydrogen ion concentration can influence the degree of calcium binding to plasma proteins. With acidosis, less calcium is bound to the plasma proteins. Conversely, with alkalosis, a greater amount of calcium is bound to the plasma proteins. Therefore, patients with alkalosis are more susceptible to hypocalcemic tetany. As with other substances in the body, the intake of calcium must be balanced with the net loss of calcium over the long term. Unlike ions such as sodium and chloride, however, a large share of calcium excretion occurs in the feces. The usual rate of dietary calcium intake is about 1000 mg/day, with about 900 mg/day of calcium excreted in the feces. Under certain conditions, fecal calcium excretion can exceed calcium ingestion because calcium can also be secreted into the intestinal lumen. Therefore, the gastrointestinal tract and the regulatory mechanisms that influence intestinal calcium absorption and secretion play a major role in calcium homeostasis. Almost all the calcium in the body (99 percent) is stored in the bone, with only about 0.1 percent in the extracellular fluid and 1.0 percent in the intracellular fluid and cell organelles. The bone, therefore, acts as a large reservoir for storing calcium and as a source of calcium when extracellular fluid calcium concentration tends to decrease. One of the most important regulators of bone uptake and release of calcium is PTH. When extracellular fluid calcium concentration falls below normal, the parathyroid glands are directly stimulated by the low calcium levels to promote increased secretion of PTH. This hormone then acts directly on the bones to increase the resorption of bone salts (release of salts from the bones) and to release large amounts of calcium into the extracellular fluid, thereby returning calcium levels back toward normal. When calcium ion concentration is elevated, PTH secretion decreases, so almost no bone resorption occurs; instead, excess calcium is deposited in the bones. Thus, the day-to-day regulation of calcium ion concentration is mediated in large part by the effect of PTH on bone resorption. The bones, however, do not have an inexhaustible supply of calcium. Therefore, over the long term, the intake of calcium must be balanced with calcium excretion by the gastrointestinal tract and the kidneys. The most important regulator of calcium reabsorption at both of these sites is PTH. Thus, PTH regulates plasma calcium concentration through three main effects: (1) by stimulating bone resorption; (2) by stimulating activation of vitamin D, which then increases intestinal reabsorption of calcium; and (3) by directly increasing renal tubular calcium reabsorption. The control of gastrointestinal calcium reabsorption and calcium exchange in the bones is discussed elsewhere, and the remainder of this section focuses on the mechanisms that control renal calcium excretion.

CONTROL OF CALCIUM EXCRETION BY THE KIDNEYS

Calcium is both filtered and reabsorbed in the kidneys but not secreted. Therefore, the rate of renal calcium excretion is calculated as “Renal calcium excretion= Calcium filtered- Calcium reabsorbed”.

Only about 60 percent of the plasma calcium is ionized, with 40 percent being bound to the plasma proteins and 10 percent complexed with anions such as phosphate. Therefore, only about 60 percent of the plasma calcium can be filtered at the glomerulus. Normally, about 99 percent of the filtered calcium is reabsorbed by the tubules, with only about 1 percent of the filtered calcium being excreted. About 65 percent of the filtered calcium is reabsorbed in the proximal tubule, 25 to 30 percent is reabsorbed in the loop of Henle, and 4 to 9 percent is reabsorbed in the distal and collecting tubules. This pattern of reabsorption is similar to that for sodium.

As is true with the other ions, calcium excretion is adjusted to meet the body’s needs. With an increase in calcium intake, there is also increased renal calcium excretion, although much of the increase of calcium intake is eliminated in the feces. With calcium depletion, calcium excretion by the kidneys decreases as a result of enhanced tubular reabsorption.

**Proximal Tubular Calcium Reabsorption**.

Most of the calcium reabsorption in the proximal tubule occurs through the paracellular pathway; it is dissolved in water and carried with the reabsorbed fluid as it flows between the cells. Only about 20% of proximal tubular calcium reabsorption occurs through the transcellular pathway in two steps. (1) Calcium diffuses from the tubular lumen into the cell down an electrochemical gradient due to the much higher concentration of calcium in the tubular lumen, compared with the epithelial cell cytoplasm, and because the cell interior has a negative charge relative to the tubular lumen. (2) Calcium exits the cell across the basolateral membrane by a calcium-ATPase pump and by sodium-calcium counter-transporter.

**Loop of Henle and Distal Tubule Calcium Reabsorption**.

In the loop of Henle, calcium reabsorption is restricted to the thick ascending limb. Approximately 50% of calcium reabsorption in the thick ascending limb occurs through the paracellular route by passive diffusion due to the slight positive charge of the tubular lumen relative to the interstitial fluid. The remaining 50% of calcium reabsorption in the thick ascending limb occurs through the transcellular pathway, a process that is stimulated by PTH. In the distal tubule, calcium reabsorption occurs almost entirely by active transport through the cell membrane. The mechanism for this active transport is similar to that in the proximal tubule and thick ascending limb and involves diffusion across the luminal membrane through calcium channels and exit across the basolateral membrane by a calcium-ATPase pump, as well as a sodium-calcium counter-transport mechanism. In this segment, as well as in the loops of Henle, PTH stimulates calcium reabsorption. Vitamin D (calcitriol) and calcitonin also stimulate calcium reabsorption in the thick ascending limb of Henle’s loop and in the distal tubule, although these hormones are not as important quantitatively as PTH in reducing renal calcium excretion.

Factors That Regulate Tubular Calcium Reabsorption.

One of the primary controllers of renal tubular calcium reabsorption is PTH. Increased levels of PTH stimulate calcium reabsorption in the thick ascending loops of Henle and distal tubules, which reduces urinary excretion of calcium. Conversely, reduction of PTH promotes calcium excretion by decreasing reabsorption in the loops of Henle and distal tubules.

In the proximal tubule, calcium reabsorption usually parallels sodium and water reabsorption and is independent of PTH. Therefore, in instances of extracellular volume expansion or increased arterial pressure— both of which decrease proximal sodium and water reabsorption—there is also reduction in calcium reabsorption and, consequently, increased urinary excretion of calcium. Conversely, with extracellular volume contraction or decreased blood pressure, calcium excretion decreases primarily because of increased proximal tubular reabsorption.

Another factor that influences calcium reabsorption is the plasma concentration of phosphate. Increased plasma phosphate stimulates PTH, which increases calcium reabsorption by the renal tubules, thereby reducing calcium excretion. The opposite occurs with reduction in plasma phosphate concentration.

Calcium reabsorption is also stimulated by metabolic alkalosis and inhibited by metabolic acidosis. Thus, acidosis tends to increase calcium excretion, whereas alkalosis tends to reduce calcium excretion. Most of the effect of hydrogen ion concentration on calcium excretion results from changes in calcium reabsorption in the distal tubule.