Name: Onoji Faith Oghenevovwero

Maric No: 17/MHS01/262

Department: Medicine and Surgery, 300l

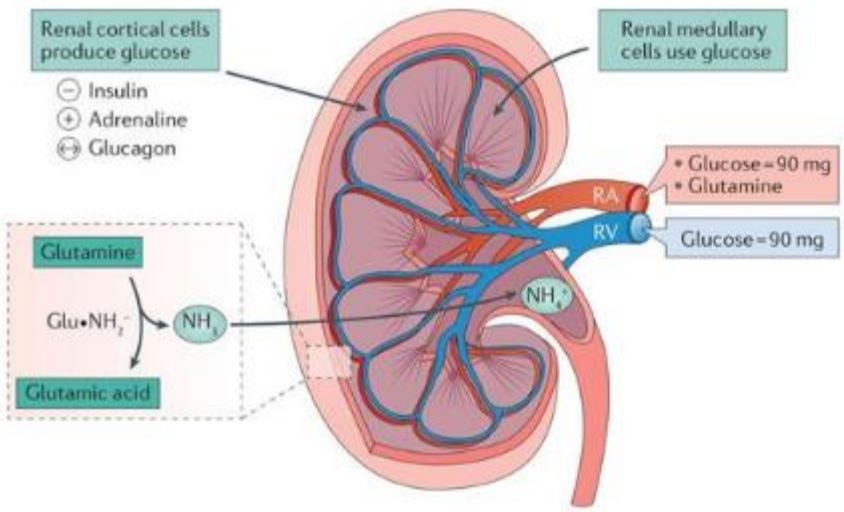
Course: Renal Physiology

Date: 24th May, 2020

The Role of Kidney in Glucose Homeostasis

Homeostasis is described the maintenance of nearly constant conditions in the internal environment. The various ions, nutrients, waste products, and other constituents of the body are normally regulated within a range of values. This includes glucose. The plasma glucose concentration is determined by the amount of glucose synthesized, and the amount removed from the circulation and metabolized. This concentration must be maintained within a relatively narrow range despite the wide daily fluctuations in glucose ingestion and glucose demands in various tissues. This can be explained by the need of the body to protect himself against hyper- and hypoglycemia and the complications that come with them. The kidneys are involved in maintaining glucose homeostasis through three different mechanisms:

- Gluconeogenesis.
- Glucose utilization.
- Reabsorption of glucose from glomerular filtrate.



Renal Gluconeogenesis

The synthesis of glucose from noncarbohydrate precursors is called gluconeogenesis (i.e. synthesis of new glucose). These precursors include lactate, amino acids, glycerol. After a 16 hour overnight fast, approximately 10 µmol ⁄ (kg /min) of glucose is released into the circulation. Almost 50% of this is the result of glycogenolysis from the liver stocks and the other half is produced by liver and kidney gluconeogenesis. The renal cortex (like the liver) contains gluconeogenic enzymes and it can synthesize glucose-6-phosphate from precursors (lactate, glutamine, glycerol and alanine). Because it contains glucose-6-phosphatase (which converts glucose-6-phosphate to glucose), it is able to release glucose into the blood stream and the human liver and kidneys are the only organs that can perform gluconeogenesis. Therefore, after an overnight fast, the liver produces 75-80% of glucose released into the circulation and the remaining 20–25% is derived from the kidneys. The liver glycogen is capable of maintaining the blood glucose concentration at normal values for 12 to 16 hours of fasting. However, beyond this, maintenance of blood glucose concentration is mainly by gluconeogenesis. Hence the liver produces 50% of glucose and the kidney 50%.

After glucose ingestion, renal gluconeogenesis increases and accounts for approximately 60% of endogenous glucose release in the postprandial (after a meal) period. Postprandial glucose levels in the plasma are determined by insulin and glucagon levels. After glucose ingestion, plasma glucose levels reach the peak in 60–90 minutes and they return to post-absorptive levels in almost 3–4 h. The plasma insulin increases four times and the plasma glucagon levels decrease by 50%. The high level of insulin increases glucose uptake by the tissues and the liver (for storage). In order to prevent hypoglycemia, renal gluconeogenesis increases.

Glucose Utilization

The cells in the renal medulla can use only glucose for their needs (like the brain) and they have enzymes capable of glucose-phosphorylation and glycolysis. They can therefore phosphorylate important amounts of glucose and accumulate glycogen but, because these cells do not have glucose-6-phosphatase or any other gluconeogenic enzymes, they are unable to release glucose into the bloodstream. In this post-absorptive (fasting) state, the kidneys utilize about 10% of all glucose utilized by the body.

Reabsorption of glucose from glomerular filtrate

The kidneys contribute to glucose homeostasis by filtering and reabsorbing glucose. In normal conditions, the kidneys can reabsorb as much glucose as possible, the result being a virtually glucose free urine. Approximately 180 grams of glucose are filtered by the glomeruli from plasma, daily but all of this quantity is reabsorbed through glucose transporters that are present in cell membranes located in the proximal tubules. These glucose transporters have a limited capacity of reabsorption. If this capacity is exceeded, glucose usually appears in the urine. The tubular maximum for glucose (TmG), the term used for the maximum capacity, can vary from 260 to 350 mg/min/1.73 m^2 in healthy subjects. It corresponds to blood glucose levels of 180-200 mg/dL. When the blood glucose is very high and the TmG is reached, the transporters cannot reabsorb all the glucose and glucosuria occurs. GLUT2 is the major transporter and it releases into circulation the glucose reabsorbed by SGLTs in the proximal tubular cells.

Clinical correlation

1. *Glycosuria*: A condition characterized by an excess of sugar in the urine, typically associated with diabetes or kidney disease. This occurs when the threshold for glucose reabsorption is reached.
2. *Hyperglycemia*: In hyperglycemia, the kidneys may play an exacerbating role by reabsorbing excess glucose, ultimately contributing to chronic hyperglycemia, which in turn contributes to chronic glycemic burden and the risk of microvascular consequences.

Micturition

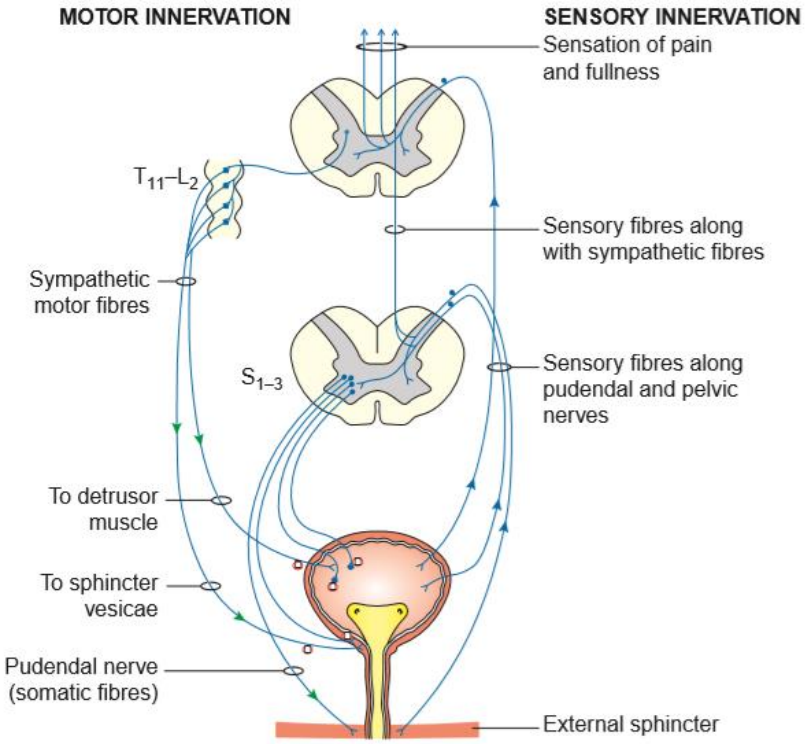
Micturition is the process by which the urinary bladder empties when it becomes filled. Ordinarily, all the urine will be emptied, with rarely more than 5 to 10 milliliters left in the bladder. This process involves two main steps:

- Filling of the bladder: the bladder fills progressively until the tension in its walls rises above a threshold level. This tension elicits the second step, which is
- Nervous reflex: This is called the micturition reflex that empties the bladder or, if this fails, at least causes a conscious desire to urinate.

The bladder is a balloon-like chamber with walls of smooth muscle collectively termed the detrusor muscle. The contraction of the detrusor muscle squeezes on the urine in the bladder lumen to produce urination. That part of the detrusor muscle at the base (or "neck") of the bladder where the urethra begins functions as the internal urethral sphincter. Just below the internal urethral sphincter, a ring of skeletal muscle found in the urogenital diaphragm surrounds the urethra. This is the external urethral sphincter, the contraction of which can prevent urination even when the detrusor muscle contracts strongly. On the posterior wall of the bladder, lying immediately above the bladder neck, is a small triangular area called the trigone. At the lowermost apex of the trigone, the bladder neck opens into the posterior urethra and the two ureters enter the bladder at the uppermost angles of the trigone. The trigone can be identified by the fact that its mucosa, the inner lining of the bladder, is smooth, in contrast to the remaining bladder mucosa, which is folded to form rugae.

Innervation of the Bladder

- *Pelvic nerves (S2 and S3)*: This is the principal nerve supply of the bladder. Coursing through the pelvic nerves are both sensory nerve fibers and motor nerve fibers. The sensory fibers detect the degree of stretch in the bladder wall while the motor nerves, which are parasympathetic fibers, innervate the detrusor muscle and causes their contraction. In addition to the pelvic nerves, two other types of innervation are important in bladder function.
- *The pudendal nerve*: This nerve supplies the external bladder sphincter. These fibers are somatic nerve fibers that innervate and control the voluntary skeletal muscle of the sphincter.
- *Hypogastric nerves*: This nerve carries sympathetic innervation from the sympathetic chain. These sympathetic fibers stimulate mainly the blood vessels and have little to do with bladder contraction. Some sensory nerve fibers also pass by way of the sympathetic nerves and may be important in the sensation of fullness and, in some instances, pain.



Filling of 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. The walls of the ureters contain smooth muscle and are innervated by both sympathetic and parasympathetic nerves 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. 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

While the bladder is filling, the parasympathetic input to the detrusor muscle is minimal, and, as a result, the muscle is relaxed. Because of the arrangement of the smooth muscle fibers, when the detrusor muscle is relaxed, the internal urethral sphincter is passively closed. Additionally, there is strong sympathetic input to the internal urethral sphincter and strong input by the somatic motor neurons to the external urethral sphincter. Therefore, the detrusor muscle is relaxed and both the internal and external sphincters are closed during the filling phase. However,

- As the bladder fills with urine, the pressure within it increases, which stimulates stretch receptors in the bladder wall.
- The afferent neurons from these receptors enter the spinal cord and stimulate the parasympathetic neurons, which then cause the detrusor muscle to contract. 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. 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. When the detrusor muscle contracts, the change in shape of the bladder pulls open the internal urethral sphincter. Simultaneously, the afferent input from the stretch receptors reflexively inhibits the sympathetic neurons to the internal urethral sphincter, which further contributes to its opening.
- In addition, the afferent input also reflexively inhibits the somatic motor neurons to the external urethral sphincter, causing it to relax.
- Both sphincters are now open, and the contraction of the detrusor muscle can produce urination.

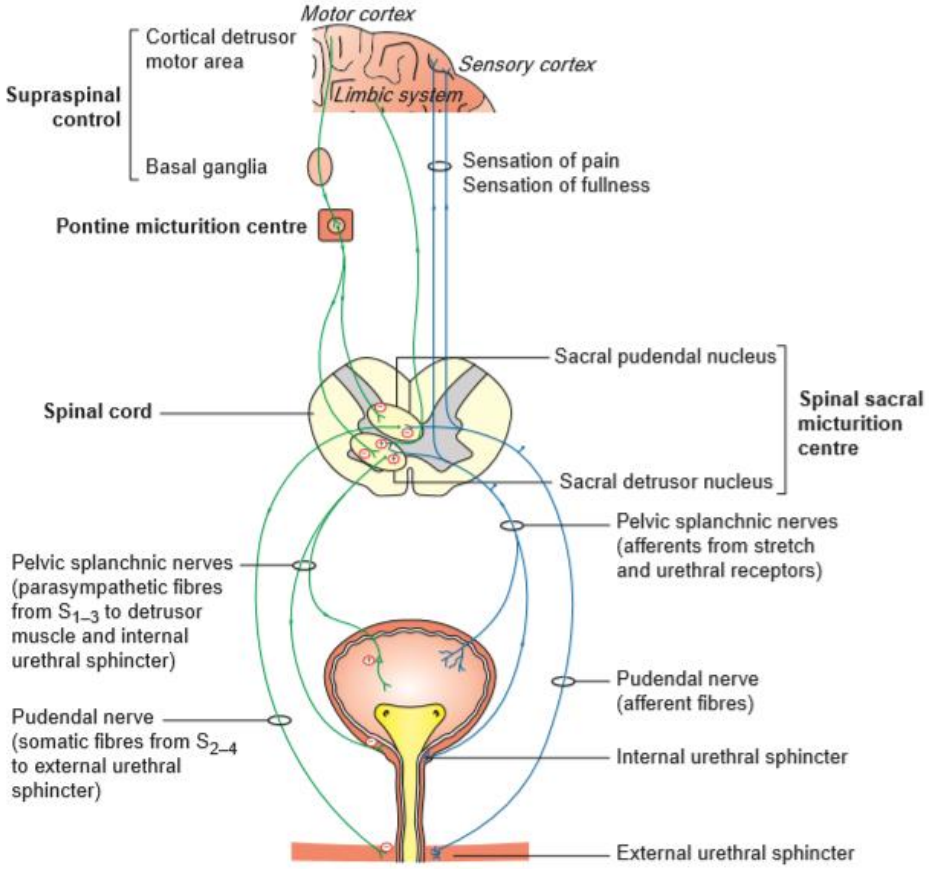
Voluntary Control of Micturition

The micturition reflex is an autonomic spinal cord reflex, but it can be inhibited or facilitated by centers in the brain. These centers include

1. Strong facilitative and inhibitory centers in the brain stem, located mainly in the pons, and
2. Several centers located in the cerebral cortex that are mainly inhibitory but can become excitatory.

The micturition reflex is the basic cause of micturition, but the higher centers normally exert final control of micturition as follows:

1. The higher centers keep the micturition reflex partially inhibited, except when micturition is desired.
2. The higher centers can prevent micturition, even if the micturition reflex occurs, by tonic contraction of the external bladder sphincter until a convenient time presents itself.
3. When it is time to urinate, the cortical centers can facilitate the sacral micturition centers to help initiate a micturition reflex and at the same time inhibit the external urinary sphincter so that urination can occur.



Clinical correlates

1. *Automatic bladder*: If spinal cord is damaged above the sacral segments but sacral segments are intact, it results into automatic bladder. This occurs after the person recovers from spinal shock following injury to the spinal cord. Recovery from the spinal shock allows the sacral centers to take over the function and typical micturition reflex returns. When bladder is full, it automatically is emptied (no voluntary control). Stimulation of skin in the genital region elicits micturition reflex.
2. *Neurogenic bladder*: Frequent and relatively uncontrollable micturition occurs when there is uninhibited neurogenic bladder. This condition results due to partial damage in the spinal cord or brain stem which interrupts most of the inhibitory signals.

Role of Kidney in Calcium homeostasis

Calcium homeostasis is the regulation of calcium ions in the blood plasma within narrow limits. The kidney is critically important in calcium homeostasis. It does this via two ways

- Reabsorption of calcium: Approximately 10 percent (100 mg/day) of the ingested calcium is excreted in the urine. About 41 percent of the plasma calcium is bound to plasma proteins and is therefore not filtered by the glomerular capillaries. The remainder is combined with anions such as phosphate (9 percent) or ionized (50 percent) and filtered through the glomeruli into the renal tubules. Normally, the renal tubules reabsorb 99 percent of the filtered calcium, and about 100 mg/day are excreted in the urine. Approximately 90 percent of the calcium in the glomerular filtrate is reabsorbed in the proximal tubules, loops of Henle, and early distal tubules. In the late distal tubules and early collecting ducts, reabsorption of the remaining 10 percent is more variable, depending on the calcium ion concentration in the blood. When calcium concentration is low, this reabsorption is great, and thus almost no calcium is lost in the urine. Conversely, even a minute increase in blood calcium ion concentration above normal increases calcium excretion markedly.
- Regulation of 1,25-Dihydroxyvitamin D3 Production: The kidneys produce the active form of vitamin D, 1,25-dihydroxyvitamin D3 (calcitriol), by hydroxylating this vitamin at the “number 1” position in the proximal convoluted tubule. This is the most active form of vitamin D. This process requires the presence of parathyroid hormone (PTH). Calcitriol is essential for normal calcium deposition in bone and calcium reabsorption by the gastrointestinal tract. The plasma concentration of

1,25-dihydroxycholecalciferol is inversely affected by the concentration of calcium in the plasma. There are two reasons for this effect. First, the calcium ion has a slight effect in preventing the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferols. Second, and even more important, the rate of secretion of PTH is greatly suppressed when plasma calcium ion concentration rises above 9 to 10 mg/100 ml. Therefore, at calcium concentrations below this level, PTH promotes the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferols in the kidneys. At higher calcium concentrations, when PTH is suppressed, the 25-hydroxycholecalciferol is converted to a different compound—24,25-dihydroxycholecalciferol— that has almost no vitamin D effect. When plasma calcium concentration is already too high, formation of 1,25-dihydroxycholecalciferol is greatly depressed. Lack of 1,25-dihydroxycholecalciferol, in turn, decreases the absorption of calcium from the intestines, bones, and renal tubules, thus causing the calcium ion concentration to fall back toward its normal level.

Clinical Correlates

- Hypocalcemia refers to low blood calcium concentration. Clinical signs of this disorder reflect increased neuromuscular excitability and include muscle spasms, tetany and cardiac dysfunction.
- Hypercalcemia indicates a concentration of blood calcium higher than normal. The normal concentration of calcium and phosphate in blood and extracellular fluid is near the saturation point; elevations can lead to diffuse precipitation of calcium phosphate in tissues, leading to widespread organ dysfunction and damage.

Juxtaglomerular Apparatus

The juxtaglomerular apparatus is a specialized structure formed by the distal convoluted tubule and the glomerular afferent arteriole. It is located near the vascular pole of the glomerulus and its main function is to regulate blood pressure and the filtration rate of the glomerulus. The Juxtaglomerular apparatus comprises three types of cells:

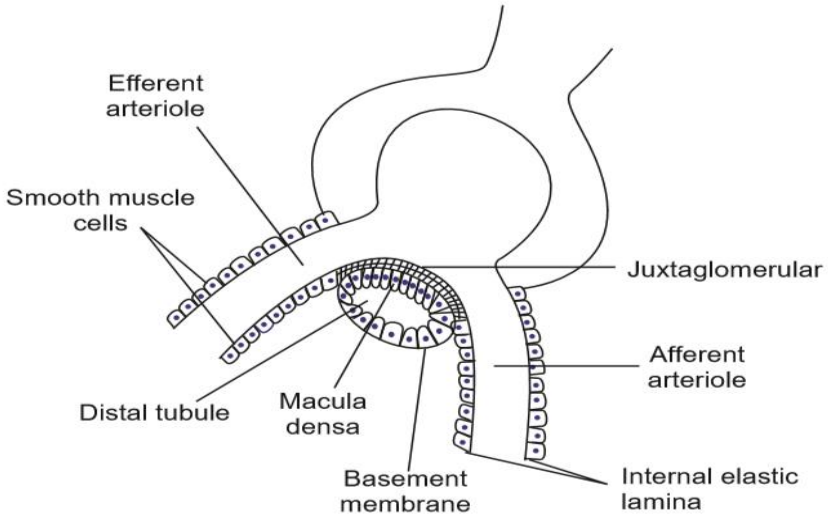
- Juxtaglomerular cells,
- Macula densa cells and
- Mesangial cells.

Juxtaglomerular cells: Juxtaglomerular cells are specialized myoepithelial (modified vascular smooth muscle) cells located in the media of the afferent arteriole in the region of Juxtaglomerular apparatus. They synthesize, store and release an enzyme called renin. They act as baroreceptors (tension receptors) and respond to changes in the transmural pressure gradient

between the afferent arterioles and the interstitial tissue. They are densely innervated by the sympathetic nerve fibers and release their renin content in response to the sympathetic discharge. They also monitor renal perfusion pressure and are stimulated by hypovolemia or decreased renal perfusion pressure.

Macula densa cells: Macula densa cells refer to the specialized renal tubular epithelial cells of a short segment of the thick ascending limb of loop of Henle which passes between the afferent and efferent arterioles supplying its glomerulus of origin. They are not well adapted for reabsorption. They are not innervated. These cells are in direct contact with the mesangial cells and in close contact with the JG cells. They act as chemoreceptors and are stimulated by decreased NaCl concentration and thereby causing increased renin release.

Mesangial cells: Mesangial cells or lacis cells are the interstitial cells of the JG apparatus. They are in contact with both the macula densa cells (on one side) and JG cells (on the other side). Functionally, these cells possibly relay the signals from macula densa to the juxtaglomerular cells after modulating the signals. In this way, a decreased intraluminal Na+ load, Cl– load, or both in the region of macula densa stimulates the Juxtaglomerular cells to secrete renin.



Role of Kidney in Regulation of Blood pressure

Arterial blood pressure is controlled by several mechanism which under normal physiological conditions will maintain the mean arterial pressure (MAP) within a narrow range of 95-100mm Hg. These mechanisms are grouped as

- Rapid blood pressure control mechanism,
- Intermediate blood pressure control mechanism and
- Long-term blood pressure control mechanism.

The kidneys play main role in the long-term control of blood pressure by the following mechanisms

- Renal-body fluid feedback mechanism
- Renin-angiotensin mechanism

Renal-body fluid feedback mechanism

The most important mechanism for the long-term control of blood pressure is linked to control of circulatory volume of the kidney. This is known as the Renal-body fluid feedback mechanism.

When blood pressure rises too high, the kidneys excrete increased quantities of sodium and water because of pressure natriuresis and pressure diuresis respectively. As a result of increased renal excretion, the extracellular fluid volume and blood volume both decrease until blood pressure returns to normal and the kidneys excrete normal amounts of sodium and water.

When blood pressure falls too low, the kidneys reduce the rate of sodium and water excretion and over a period of hours to days, if the person drinks enough water and eats enough salts to increase blood volume, the blood pressure will return to its previous level. This mechanism being very slow to act, is not of major importance in the acute control of arterial blood pressure. However, it is by far the most potent of all long-term arterial pressure controllers.

Renin-angiotensin Mechanism

Consistent and long-term control of blood pressure is determined by the renin-angiotensin system. Renin is a protein enzyme released by the Juxtaglomerular cells of 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. When blood pressure decreases there will be a drop in renal blood flow and/or a decreased concentration of Na^+, this will stimulate the volume receptors found in the juxtaglomerular apparatus of the kidney to release renin. Most of the renin enters the renal blood and then passes out of the kidneys to circulate throughout the entire body. Renin acts enzymatically on another plasma protein, called angiotensinogen, to release angiotensin I. Angiotensin I has mild vasoconstrictor properties but not enough to cause significant changes in circulatory function. Within a few seconds to minutes after formation of angiotensin I, it is

converted to 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 angiotensin converting 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 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. The second principal means by which angiotensin II increases the arterial pressure is to decrease excretion of both salt and water by the kidneys. Angiotensin II also causes the adrenal glands to secrete aldosterone, and the aldosterone in turn increases salt and water reabsorption by the kidney tubules.

Clinical correlates

- *Renal hypertension*: Renal hypertension, also called renovascular hypertension, is elevated blood pressure caused by kidney disease. It can usually be controlled by blood pressure drugs. Renal hypertension is caused by a narrowing in the arteries that deliver blood to the kidney. When the kidneys receive low blood flow, they act as if the low flow is due to dehydration. So, they respond by releasing hormones that stimulate the body to retain sodium and water. Blood vessels fill with additional fluid, and blood pressure goes up.