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COLLEGE: MEDICAL AND HEALTH SCIENCES

DEPARTMENT: MEDICINE AND SURGERY

LEVEL: 300

ASSIGNMENT

Course title: renal physiology body fluid and temperature regulation

Course code: PHS 303

Question assignment

1. Discuss the role of kidney in glucose homeostasis
2. Discuss the process of micturition
3. Explain juxtaglomerular apparatus
4. Discuss the role of kidney in regulation of blood pressure
5. Discuss the role of kidney in calcium homeostasis

Question one

Discuss the role of kidney in glucose homeostasis

The primary function of the kidney is to maintain homeostasis, and this is accomplished by the formation of urine. During the formation of urine, kidneys regulate various activities in the body, which are concerned with homeostasis.

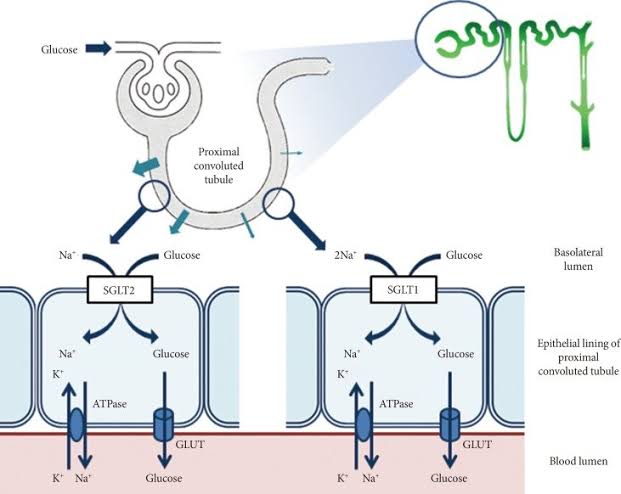
ROLE OF KIDNEY IN GLUCOSE HOMEOSTASIS

Nutritional substances in the blood, such as glucose, amino acids are freely filtered at the glomerular capillaries but are not excreted into the urine because approximately all the filtered substance is reabsorbed from the proximal tubules back into the blood. This allows these nutritional substances to be conserved in the body fluids.

* **Reabsorption of Glucose**

Glucose is completely reabsorbed in the proximal convoluted tubule. It is transported by secondary active transport (sodium cotransport) mechanism.

Glucose and sodium bind to a common carrier protein in the luminal membrane of tubular epithelium and enter the cell. The carrier protein is called **sodium-dependent glucose cotransporter 2 (SGLT2)**. From tubular cell, glucose is transported, through the basolateral membrane through facilitated diffusion, into renal medullary interstitial fluid by another carrier protein called **glucose transporter (Glut 1 and GluT2).**



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Tubular maximum for glucose (TmG)

In adult male, TmG is 375 mg/minute and in adult females it about 300 mg/minute.

Renal threshold for glucose

Renal threshold for glucose is 180 mg/dL in venous blood.

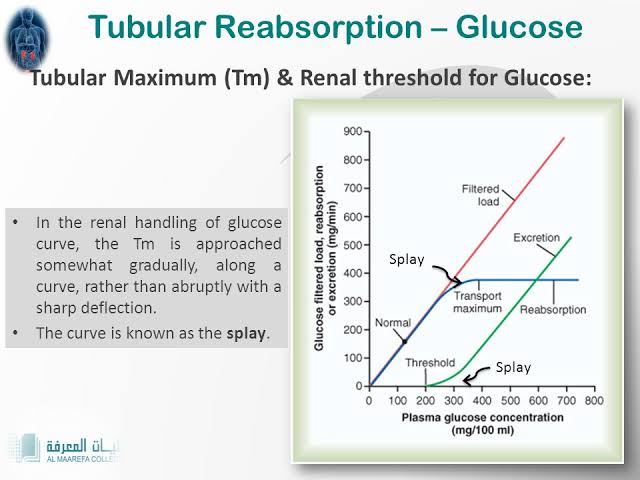
At low levels of plasma glucose, no glucose is filtered through the glomerular filtration. When the blood level reaches 180 mg/dL glucose is not reabsorbed completely and appears in urine.

Splay

Splay means deviation. With normal Glomerular Filtration Rate (GFR) of 125 mL/ minute and TmG of 375 mg/minute in an adult male the predicted (expected) renal threshold for glucose should be 300 mg/dL. But actually(reality) it is only 180 mg/dL.

When the renal threshold curves are drawn by using these values, the actual curve deviates from the ‘should be’ or predicted or ideal curve. This type of deviation is called splay.

Splay is because of the fact that all the nephrons do not have the same filtering and reabsorbing capacities and tubular maximum for glucose, TmG, therefore some nephrons may excrete before others.

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* **Glucose Synthesis**

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. The glucose produced is used for covering the energy needs of the medulla.

Gluconeogenesis occurs mainly in the cytosol although some precursors are produced in the mitochondria. Liver is the major tissue for gluconeogenesis. During starvation, the kidney’s cortex is also capable of making glucose by gluconeogenesis. Certain enzymes required in gluconeogenesis are present only in these organs.

IN SUMMARY

* The kidneys freely filter glucose at the glomerular capillaries but are not excreted into the urine because approximately all the filtered substance is reabsorbed from the proximal tubules back into the blood. This allows for glucose to be conserved in the body fluids.
* At low levels of plasma glucose, no glucose is filtered through the glomerular filtration. When the blood level reaches 180 mg/dL glucose is not reabsorbed completely and appears in urine.
* Thus, by excreting extra amount of sugar in the urine during hyperglycemic state and reabsorbing sugar during the hypoglycemic state, the kidney helps in regulating the level of glucose in blood.
* During starvation, the kidney is also capable of making glucose by gluconeogenesis.

APPLIED PHYSIOLOGY

**GLYCOSURIA**

Normally, the urine contains about 0.05 gm% of sugar. Such a small quantity cannot be detected by Benedict’s test, but under certain circumstances, a considerable amount of glucose or other sugar may be excreted in the urine.

Excretion of detectable amount of sugar in urine is known as **glycosuria**. Glycosuria results from the rise of blood glucose above its renal threshold level (180 mg%).

Glycosuria may be due to various reasons on the basis of which it is classified into the following groups:

1. Alimentary (lag storage) glycosuria

2. Renal glycosuria

3. Diabetic glycosuria.

**Renal Glycosuria**

This is observed due to impaired tubular reabsorption of glucose and have lowered renal threshold (may be 130-150 mg%) for glucose.

In such cases, the blood glucose level is below 180 mg%, i.e. below normal renal threshold for glucose, but glucose appears in the urine due to lowered renal threshold.

Renal glycosuria is a benign condition, unrelated to diabetes and it may occur temporarily in pregnancy without symptoms of diabetes.

CAUSE: Renal glycosuria may result from inherited defects in the kidney or it may be acquired as a result of kidney disease.

Question two

Discuss the process of micturition

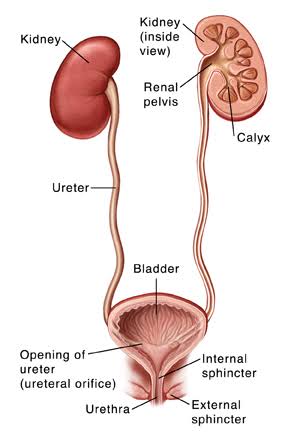
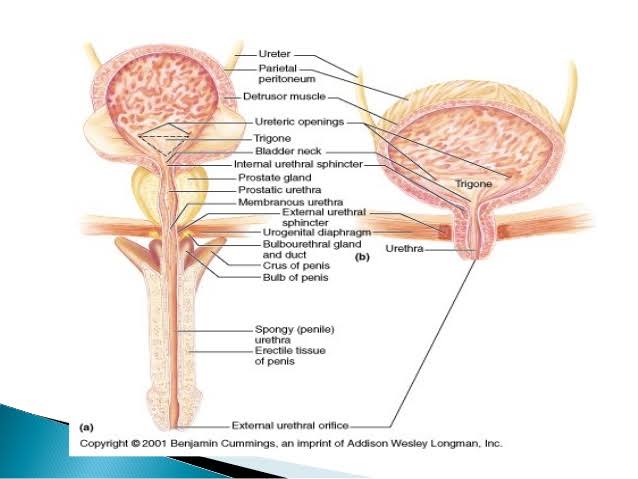
MICTURITION

Micturition, also known as urination, is a process by which urine is voided from the urinary bladder. It is the process by which the urinary bladder empties when it becomes filled.

URINART TRACT

Urine is continually produced but not continually released from the body. Certain structures for storage and neurological input allow for a timely release. These structures are:

1. **Ureters**: are long, narrow ducts, usually about 25 to 35cm long in adults, that carry urine from the kidneys to the bladder. They enter into the urinary bladder through the detrusor muscle in the trigone region of the bladder.
2. **Urinary bladder**: a triangular, elastic muscular hollow organ located in the pelvic cavity (when empty) or lower abdomen (when full). It stores urine prior to disposal by micturition. Urine enters the bladder via the ureters and exits via the urethra.
3. **Urethra**: a tube that coveys’ urine out of the body, and, in male penis, is also the tube through which semen is ejaculated. The male urethra is about 20cm long and the female urethra is about 3 to 4cm long.

There are two urethra sphincters in the urinary tract:

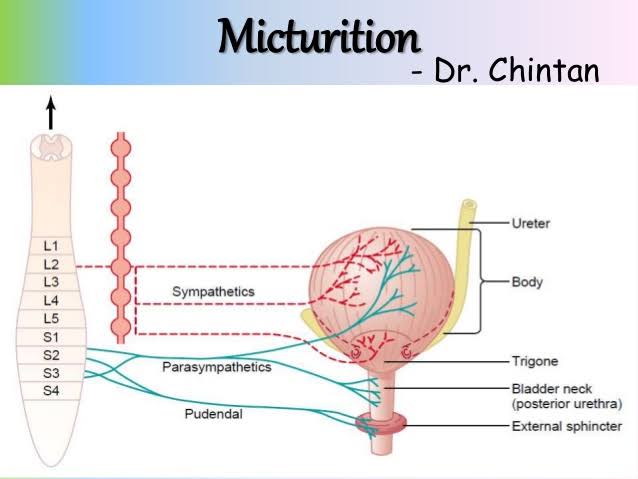
1. **Internal urethral sphincter**: located between the neck of the bladder and upper end of urethra. It is formed by the thickening of detrusor muscle (smooth muscle fibers interlaced with a large amount of elastic tissue). It is innervated by autonomic nerve fibers. It normally prevents emptying of the bladder until the pressure in the main parts of the bladder rises above a critical threshold and closes the urethra when bladder is emptied.
2. **External urethral sphincter**: it is located in the urogenital diaphragm. It is made up of voluntary, circular skeletal muscle fibres. It is innervated by somatic nerve fibers. It is used to consciously prevent urination even when involuntary controls are attempting to empty the bladder.

INNERVATION OF THE URINARY BLADDER AND SPHINCTER

Urinary bladder and internal sphincters are supplied by **sympathetic fibers (through the hypogastric nerves) and parasympathetic fibers (via the pelvic nerves)**.

External sphincter is supplied by the **somatic nerve fibers (through the pudendal nerve)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| NERVE | Action on Detrusor muscle | Action on internal sphincter | Action on external sphincter | FUNCTION |
| **Sympathetic** (hypogastric) nerve | Relaxation | Constriction | Not supplied | Filling of urinary bladder |
| **Parasympathetic** (pelvic) nerve | Contraction | Relaxation | Not supplied | Emptying of urinary bladder |
| **Somatic**(pudendal) nerve | Not supplied | Not supplied | Constriction | Voluntary control of micturition |



Innervation of urinary bladder and sphincters

**PROCESS OF MICTURITION**

Micturition is a reflex process. However, in grown up children and adults, it can be controlled voluntarily to some extent. 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.

Micturition involves **two main steps**:

* First, the bladder fills progressively until the tension in its walls rises above a threshold level; this elicits the second step
* The second step is a nervous reflex called the micturition reflex that empties the bladder or, if this fails, at least causes a conscious desire to urinate.

STEP 1: FILLING OF URINARY BLADDER

Urine is continuously formed by nephrons and it flows into urinary bladder drop by drop through ureters.

When urine collects in the pelvis of ureter, the contraction sets up in pelvis. This contraction is transmitted through rest of the ureter in the form of peristaltic wave up to trigone of the urinary bladder. Peristaltic wave usually travels at a velocity of 3 cm/second. It develops at a frequency of 1 to 5 per minute. The peristaltic wave moves the urine into the bladder. After leaving the kidney, the direction of the ureter is initially downward and outward. Then, it turns horizontally before entering the bladder.

At the entrance of ureters into urinary bladder, a valvular arrangement is present. When peristaltic wave pushes the urine towards bladder, this valve opens towards the bladder. The position of ureter and the valvular arrangement at the end of ureter prevent the back flow of urine from bladder into the ureter when the detrusor muscle contracts. Thus, urine is collected in bladder drop by drop.

A reasonable volume of urine can be stored in urinary bladder without any discomfort and without much increase in pressure inside the bladder (intravesical pressure). It is due to the adaptation of detrusor muscle. This can be explained by **cystometrogram**.

**CYSTOMETROGRAM**

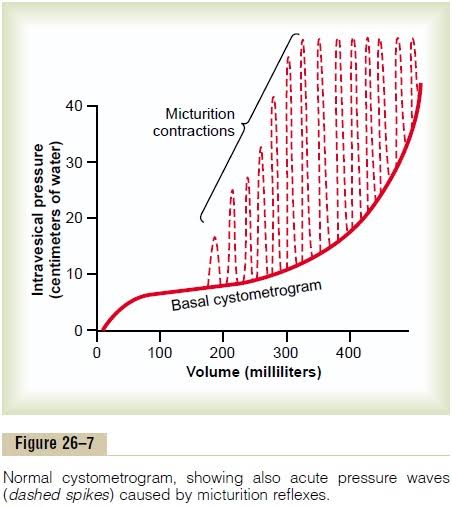
**Cystometry** is the technique used to study the relationship between intravesical pressure and volume of urine in the bladder.

**Cystometrogram** is the graphical registration (recording) of pressure changes in urinary bladder in relation to volume of urine collected in it.

Method of Recording Cystometrogram

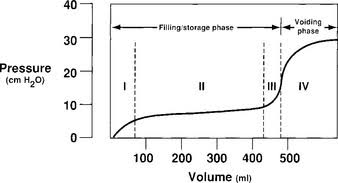
A double lumen catheter is introduced into the urinary bladder. One of the lumens is used to infuse fluid into the bladder and the other one is used to record the pressure changes by connecting it to a suitable recording instrument.

First, the bladder is emptied completely. Then, a known quantity of fluid is introduced into the bladder at regular intervals. The intravesical pressure developed by the fluid is recorded continuously. A graph is obtained by plotting all the values of volume and the pressure. This graph is the cystometrogram.



Description of Cystometrogram

Cystometrogram shows three segments: -



**Segment I**

Initially, when the urinary bladder is empty, the intravesical pressure is about zero (0). When about 100 mL of fluid is collected, the pressure rises sharply to about 10cm H2O.

At this point, the desire for micturition occurs. The desire for micturition is associated with a vague feeling in the perineum, but it can be controlled voluntarily.

**Segment II**

Segment II shows the plateau, i.e. the intravesical pressure was kept at a constant level. It remains at 10cm H2O even after introducing 300 to 400 mL of fluid. It is because of adaptation of urinary bladder by relaxation. It is in accordance with law of Laplace.

According to the law of Laplace, the pressure in a spherical organ is inversely proportional to its radius, the tone remaining constant. That is, if radius is more, the pressure is less and if radius is less the pressure is more, provided the tone remains constant.

P = T/R, where P is pressure, T is tension and R is radius.

Accordingly, in the bladder, the tension increases as the urine is filled. At the same time, the radius also increases due to relaxation of detrusor muscle. Because of this, the pressure does not change and plateau appears in the graph.

**Segment III**

Beyond the 400mL, collection of more fluid in the bladder causes the intravesical pressure to rise sharply. As the pressure increases, the contraction of detrusor muscle becomes intense, increasing the consciousness and the urge for micturition. Still, voluntary control is possible up to volume of 600 to 700 mL at which the pressure rises to about 35 to 40cm H2O.

When the intravesical pressure rises above 40 cm water, the contraction of detrusor muscle becomes still more intense. And, voluntary control of micturition is not possible. Now, pain sensation develops and micturition is a must at this stage.

STEP 2: MICTURITION REFLEX

Micturition reflex is the reflex by which micturition occurs. This reflex is elicited by the stimulation of stretch receptors situated on the wall of urinary bladder and urethra. When about 300 to 400 mL of urine is collected in the bladder, intravesical pressure increases. This stretches the wall of bladder resulting in stimulation of stretch receptors and generation of sensory impulses.

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.

* **Pathway for Micturition Reflex**

When about 300 to 400mL of urine is collected in the bladder, intravesical pressure increases. This stretches the wall of the bladder, resulting in stimulation of the sensory stretch receptors in the bladder wall and generation of sensory impulses.

The sensory (afferent) impulses from the bladder’s stretch receptors are conducted to the sacral segments of the cord through the sensory fires of the pelvic (parasympathetic) nerves. Motor (efferent) impulses produced in spinal cord, are then reflexively conducted to the bladder and internal sphincters through motor fibers of pelvic (parasympathetic) nerve.

Motor impulses cause contraction of detrusor muscle and relaxation of internal sphincter so that, urine enters the urethra from the bladder.

When the bladder is only partially filled, these micturition contractions usually relax spontaneously after a fraction

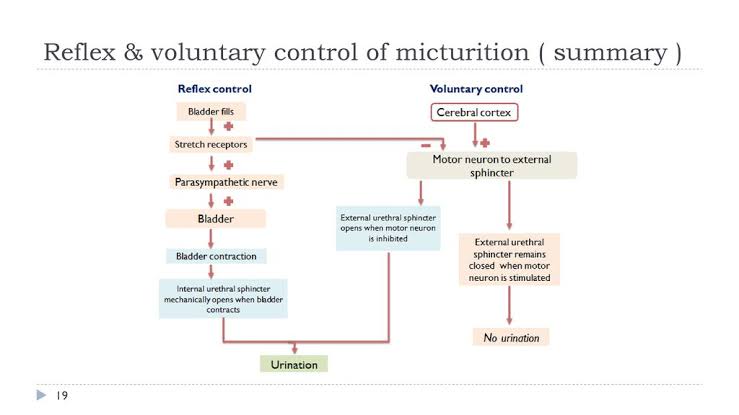
o the external sphincter to inhibit it (i.e. causes the external sphincter to relax).

If this inhibition is more potent in the brain than the voluntary constrictor signals to the external sphincter, then the external sphincter would relax and urination will occur. If not, urination will not occur until the bladder fills still further and the micturition reflex becomes more powerful.

Once a micturition reflex begins, it is "self-regenerative". That is, initial contraction of the bladder activates the stretch receptors to cause still further increase in sensory impulses from the bladder and posterior urethra, which then 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 and urine is voided out completely. During micturition, the flow of urine is facilitated by the increase in the abdominal pressure due to the voluntary contraction of abdominal muscles.

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.

It is important to note that 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.



* **Higher Centers for Micturition (Facilitation or Inhibition of Micturition by the Brain)**

The micturition reflex is an autonomic spinal cord reflex, but is regulated by higher centers. The higher centers, which control micturition are of two types, inhibitory centers and facilitatory centers.

Inhibitory centers for micturition

* Strong inhibitory centers are located in the brain stem, mainly in the pons and mid-brain.
* Several centers located in the cerebral cortex are mainly inhibitory.

They inhibit micturition by suppressing spinal micturition centers.

Facilitatory centers for micturition

* Strong facilitative centers in the brain stem, located mainly in the pons.
* Some centers in the cerebral cortex.

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.

Voluntary urination is usually initiated in the following way:

First, a person voluntarily contracts his or her abdominal muscles, which increases the pressure in the bladder and allows extra urine to enter the bladder neck and posterior urethra under pressure, thus stretching their walls. This stimulates the stretch receptors, which excites the micturition reflex and simultaneously inhibits the external urethral sphincter.

Ordinarily, all the urine will be emptied, with rarely more than 5 to 10 mL left in the bladder.

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APPLIED PHYSIOLOGY

1. **Atonic Bladder and Incontinence Caused by Destruction of Sensory Nerve Fibers**

Atonic bladder is the urinary bladder with loss of tone in detrusor muscle. It is also **called flaccid neurogenic bladder or hypoactive neurogenic bladder**. It is caused by destruction of sensory (pelvic) nerve fibers of urinary bladder.

Micturition reflex contraction cannot occur if the sensory nerve fibers from the bladder to the spinal cord are destroyed, thereby preventing transmission of stretch signals from the bladder. Due to the destruction of sensory nerve fibers, the bladder is filled without any stretch signals to spinal cord. Due to the absence of stretch signals, detrusor muscle loses the tone and becomes flaccid. When this happens, a person loses bladder control, despite intact efferent fibers from the cord to the bladder and despite intact neurogenic connections within the brain. Instead of emptying periodically, the bladder fills to capacity and overflows a few drops at a time through the urethra. This is called **overflow incontinence or overflow dribbling**

Conditions/ causes of Destruction of Sensory Nerve Fibers

1. Injury to the sacral region of the spinal cord: During the first stage (stage of spinal shock) after injury to sacral segments of spinal cord the bladder becomes atonic.
2. Syphilis: Syphilis results in the degenerative nervous disorder called **tabes dorsalis**, which is characterized by the degeneration of dorsal (sensory) nerve roots (syphilis can cause constrictive fibrosis around the dorsal root nerve fibers, destroying them.). Degeneration of sensory nerve roots of sacral region develops atonic bladder. The atonic bladder in tabes dorsalis is called **tabetic bladder.**
3. **Automatic bladder Caused by Spinal Cord Damage Above the Sacral Region**

Automatic bladder is the urinary bladder characterized by hyperactive micturition reflex with loss of voluntary control. So, even a small amount of urine collected in the bladder elicits the micturition reflex resulting in emptying of bladder.

It is caused by spinal cord damage above the sacral region. If the spinal cord is damaged above the sacral region but the sacral cord segments are still intact, typical micturition reflexes can still occur. However, they are no longer controlled by the brain, hence the voluntary control is lacking because of absence of inhibition or facilitation of micturition by higher centers.

This occurs during the second stage (stage of recovery) after complete transection of spinal cord above the sacral segments. During the first few days to several weeks after the damage to the cord has occurred (first stage of spinal shock) the micturition reflexes are suppressed because of the state of "spinal shock" caused by the sudden loss of facilitative impulses from the brain stem and cerebrum. The urinary bladder loses the tone and becomes atonic resulting in overflow incontinence.

However, if the bladder is emptied periodically by catheterization to prevent bladder injury caused by overstretching of the bladder, the excitability of the micturition reflex gradually increases until typical micturition reflexes return; at this second stage after shock period, the micturition reflex returns. However, the voluntary control is lacking because of absence of inhibition or facilitation of micturition by higher centers. Periodic (but unannounced) bladder emptying occurs. Some patients can still control urination in this condition by stimulating the skin (scratching or tickling) in the genital region, which sometimes elicits a micturition reflex.

There is hypertrophy of detrusor muscles so that the capacity of bladder reduces. Some patients develop hyperactive micturition reflex.

1. **Uninhibited neurogenic bladder Caused by Lack of Inhibitory Signals from the Brain**

Another abnormality of micturition is the so-called uninhibited neurogenic bladder. Uninhibited neurogenic bladder is the urinary bladder with frequent and relatively uncontrolled micturition.

This condition derives from partial damage in the spinal cord or the brain stem that interrupts most of the inhibitory signals, mostly as a result of lesion in midbrain. Therefore, facilitative impulses passing continually down the cord keep the sacral centers so excitable that even a small quantity of urine elicits an uncontrollable micturition reflex, thereby promoting frequent and uncontrollable urination.

It is also called **spastic neurogenic bladder** or **hyperactive neurogenic bladder**.

1. **Nocturnal micturition**

Nocturnal micturition is the involuntary voiding of urine during night. It is otherwise known as **enuresis or bedwetting**. It occurs due to the absence of voluntary control of micturition. It is a common and normal process in infants and children below 3 years. It is because of incomplete myelination of motor nerve fibers of the bladder. When myelination is complete, voluntary control of micturition develops and bedwetting stops.

If nocturnal micturition occurs after 3 years of age it is considered abnormal. It occurs due to neurological disorders like lumbosacral vertebral defects. It can also occur due to psychological factors. Loss of voluntary control of micturition occurs even during the impairment of motor area of cerebral cortex.

Question three

Explain juxtaglomerular apparatus

JUXTAGLOMERULAR APPARATUS (JGA)

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

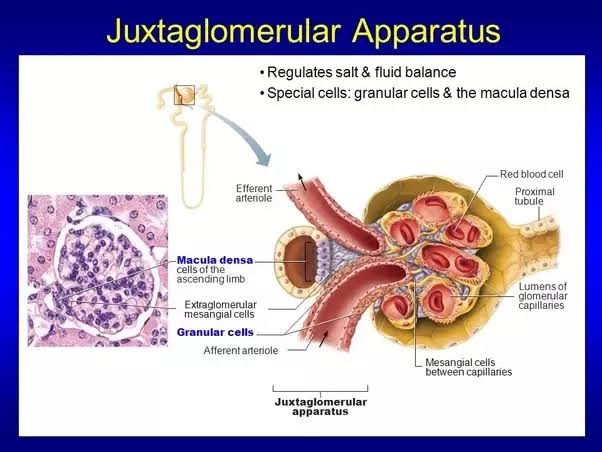
STRUCTURE OF JUXTAGLOMERULAR APPARATUS

Juxtaglomerular apparatus is formed by three different structures:

1. Macula densa

2. Extraglomerular mesangial cells

3. Juxtaglomerular cells.



1. **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, but is very close to afferent arteriole. Macula densa is formed by tightly packed cuboidal epithelial cells and contains Golgi apparatus.

1. **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**

The 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.

They are phagocytic in nature.

These cells also secrete glomerular interstitial matrix, prostaglandins and cytokines.

1. **JUXTAGLOMERULAR CELLS (JG 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 (renin) in their cytoplasm.

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

1. **Secretion of hormones**: Primary function of juxtaglomerular apparatus is the secretion of hormones.
2. **Regulation of glomerular blood flow and glomerular filtration rate (GFR)**: The JGA is also one of the components of the tubuloglomerular feedback mechanism that is involved in autoregulation of the glomerular blood flow and glomerular filtration rate.
3. SECRETION OF HORMONES

Juxtaglomerular apparatus secretes two hormones:

1. Renin

2. Prostaglandin.

**1. RENIN**

Renin is a peptide with 340 amino acids. Along with angiotensin, it forms the Renin-Angiotensin System (RAS), a hormone system that plays an important role in the maintenance of blood pressure.

Renin is secreted by Juxtaglomerular cells of the JGA.

Stimulants for renin secretion

Secretion of renin is stimulated by four factors:

1. Fall in arterial blood pressure: This is directly sensed mechanically by the juxtaglomerular cells.
2. Reduction in the ECF volume
3. Increased sympathetic activity: Nerves lie on the tunica externa of the blood vessels. These sympathetic nerves have their nerve endings on the juxtaglomerular cells. Their stimulation causes these cells to release renin.
4. Decreased load of sodium and chloride in macula densa.: the macula densa cells senses low sodium and chloride ions in the distal convoluted tubules and interprets it as low blood pressure in the glomerulus and in the circulatory system. Hence, they send signals to the JG cells to release renin.

Renin-angiotensin system (RAS)

The renin-angiotensin system is a powerful mechanism for controlling arterial pressure.

When renin is released into the blood, it acts on a specific plasma protein called **angiotensinogen or renin substrate**. Angiotensinogen is an alpha-2 globulin and has 452 amino acids. By the activity of renin, the angiotensinogen is converted into a 10-amino acid peptide, **angiotensin-I**. Angiotensin-I is converted into **angiotensin II**, an 8-amino acid peptide, by the activity of angiotensin-converting enzyme (ACE) secreted from lungs. Most of the conversion of angiotensin I into angiotensin II takes place in lungs. Other tissues that have ACE are kidneys and blood vessels.

Angiotensin II is an extremely powerful vasoconstrictor. It has a short half-life of about 1 to 2 minutes. Then it is rapidly degraded into a 7-amino acid peptide called **angiotensin III** by angiotensinases, which are present in RBCs and vascular beds in many tissues. Angiotensin III is converted into **angiotensin IV**, which is a 6-amino acid peptide.

Actions of Angiotensin

* Angiotensin I

Angiotensin-I is physiologically inactive and serves only as the precursor of angiotensin II.

* Angiotensin II

Angiotensin II is the most active form. Its actions include:

* On blood vessels:

1. Angiotensin II increases arterial blood pressure by directly acting on the blood vessels and causing vasoconstriction. It is a potent constrictor of arterioles. Earlier, when its other actions were not found it was called **hypertensin**.
2. It increases blood pressure indirectly by increasing the release of noradrenaline from postganglionic sympathetic fibers. Noradrenaline is a general vasoconstrictor.

* On adrenal cortex:

It stimulates zona glomerulosa of adrenal cortex to secrete aldosterone. Aldosterone acts on renal tubules and increases retention of sodium, which is also responsible for elevation of blood pressure.

* On kidney:

1. Angiotensin II regulates glomerular filtration rate by two ways:
2. It constricts the efferent arteriole, which causes decrease in filtration after an initial increase.
3. It contracts the glomerular mesangial cells leading to decrease in surface area of glomerular capillaries and filtration.
4. It increases sodium reabsorption from renal tubules. This action is more predominant on proximal tubules.

* On brain:

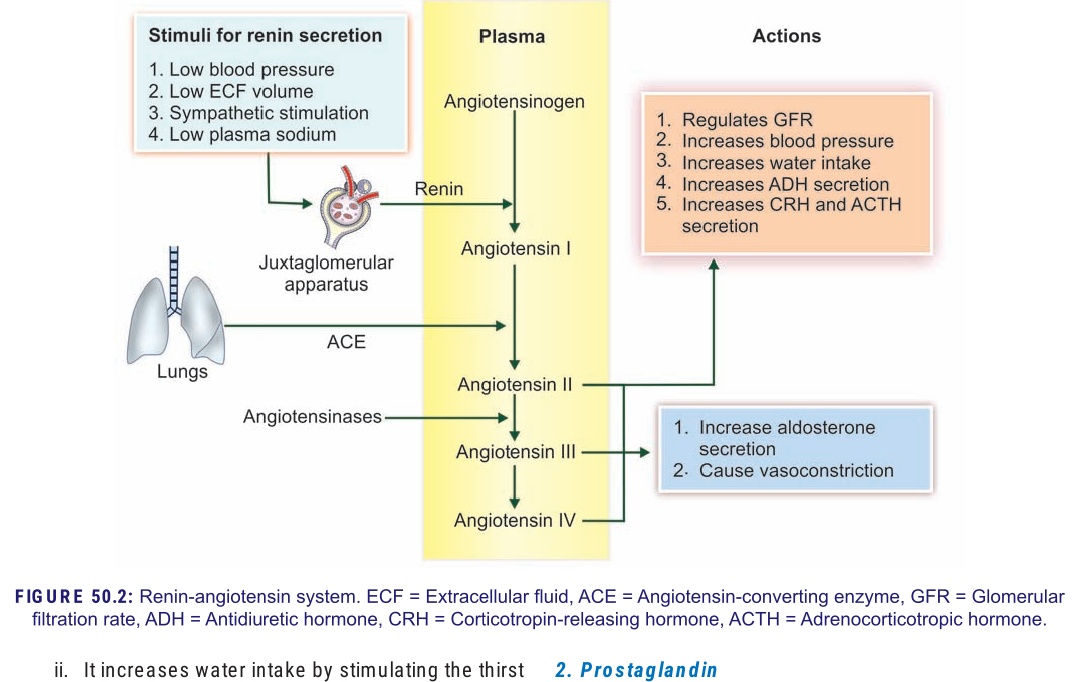
1. Angiotensin II inhibits the baroreceptor reflex and thereby indirectly increases the blood pressure. Baroreceptor reflex is responsible for decreasing the blood pressure.
2. It increases water intake by stimulating the thirst center
3. It increases the secretion of corticotropin-releasing hormone (CRH) from hypothalamus. CRH in turn increases secretion of adrenocorticotropic hormone (ACTH) from pituitary.
4. It increases secretion of antidiuretic hormone (ADH) from hypothalamus.

* Angiotensin II acts as a growth factor in heart and it is thought to cause muscular hypertrophy and cardiac enlargement.
* Angiotensin III

Angiotensin III increases the blood pressure and stimulates aldosterone secretion from adrenal cortex. It has 100% adrenocortical stimulating activity and 40% vasopressor activity of angiotensin II.

* Angiotensin IV

It also has adrenocortical stimulating and vasopressor activities.



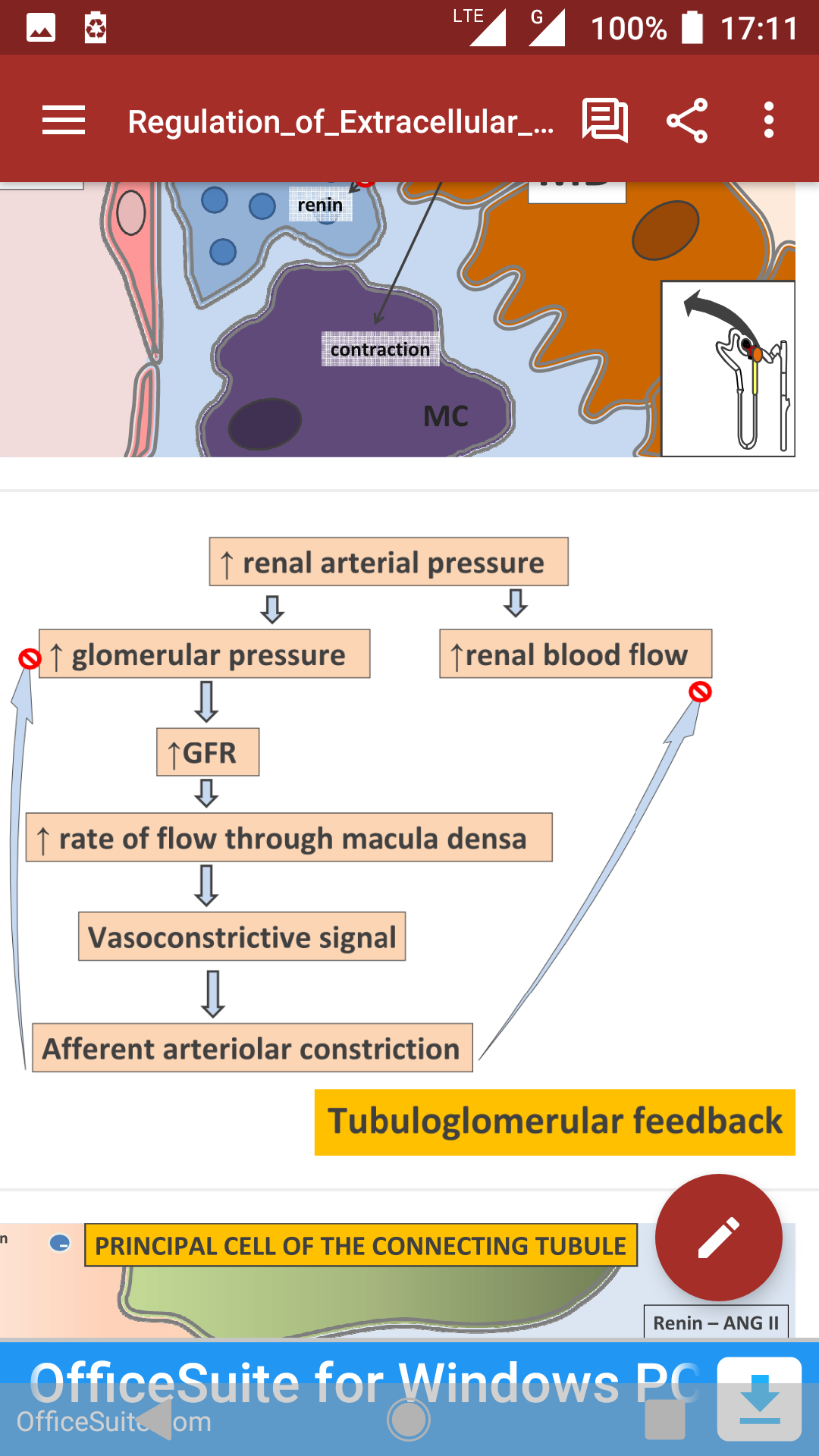
**2. PROSTAGLANDIN**

Extraglomerular mesangial cells of juxtaglomerular apparatus secrete prostaglandin.

Prostaglandin is also secreted by interstitial cells of medulla called type I medullary interstitial cells.

1. 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.



CLINICAL SIGNIFICANCE

Excess secretion of renin by the juxtaglomerular cells can lead to excess activity of the renin-angiotensin system, hypertension and an increase in blood volume. This is not responsive to the usual treatment for essential hypertension, namely medications and lifestyle modification.

Question four

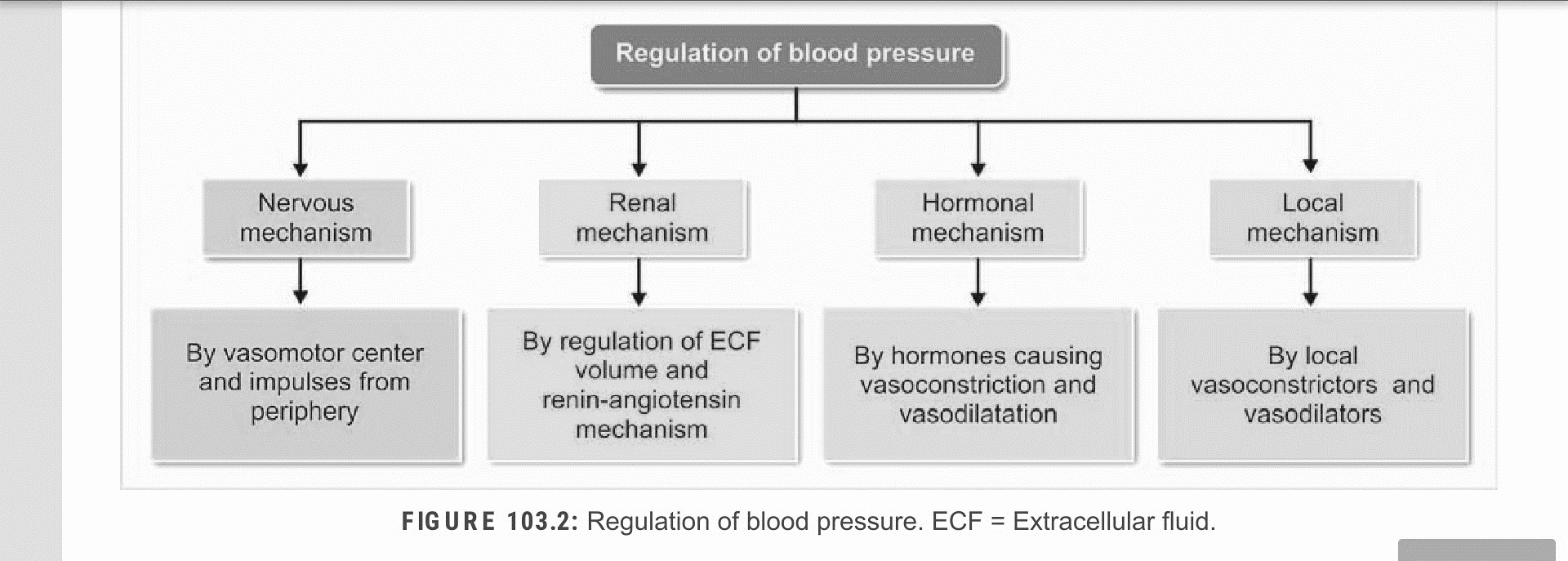
Discuss the role of kidney in regulation of blood pressure

REGULATION OF ARTERIAL BLOOD PRESSURE

Arterial blood pressure varies even under physiological conditions. However, immediately it is brought back to normal level because of the presence of well-organized regulatory mechanisms in the body.

These regulatory mechanisms are:

1. Nervous mechanism or short-term regulatory mechanism
2. Renal mechanism or long-term regulatory mechanism
3. Hormonal mechanism
4. Local mechanism



RENAL MECHANISM FOR REGULATION OF BLOOD PRESSURE – LONG-TERM REGULATION

Kidneys play an important role in the long-term regulation of arterial blood pressure.

When blood pressure alters slowly in several days/months/years, the nervous mechanism adapts to the altered pressure and loses the sensitivity for the changes. It cannot regulate the pressure anymore. In such conditions, the renal mechanism operates efficiently to regulate the blood pressure. Therefore, it is called long-term regulation.

Kidneys regulate arterial blood pressure by two ways:

1. By regulation of ECF volume

2. Through renin angiotensin mechanism.

1. **BY REGULATION OF EXTRACELLULAR FLUID VOLUME (Renal-Body Fluid System for Arterial Pressure Control)**

The renal-body fluid system for arterial pressure control acts slowly but powerfully as follows:

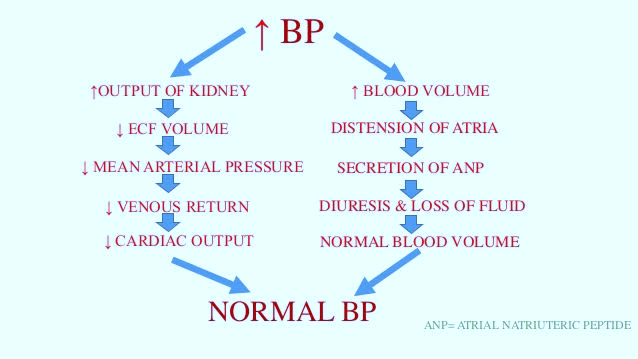
* Increase in extracellular fluid (ECF) volume, due to excess intake of water and salt or excess intake of salt and increase of water osmotically, would result in increase in blood volume. If blood volume increases and vascular capacitance is not altered, arterial pressure will also increase. The increase in pressure would in turn cause the kidneys to excrete the excess volume, i.e. excrete large amounts of water and salt, particularly sodium, by means of pressure diuresis and pressure natriuresis.

**Pressure diuresis** is the excretion of large quantity of water in urine because of increased blood pressure. Even a slight increase in blood pressure in humans of only a few mm Hg can double renal output of water i.e. doubles the water excretion. **Pressure natriuresis** is the excretion of large quantity of sodium in urine. A slight increase in blood pressure can also double the output of salt.

Because of diuresis and natriuresis, there is a decrease in ECF volume and blood volume, which in turn brings the arterial blood pressure back to normal level.

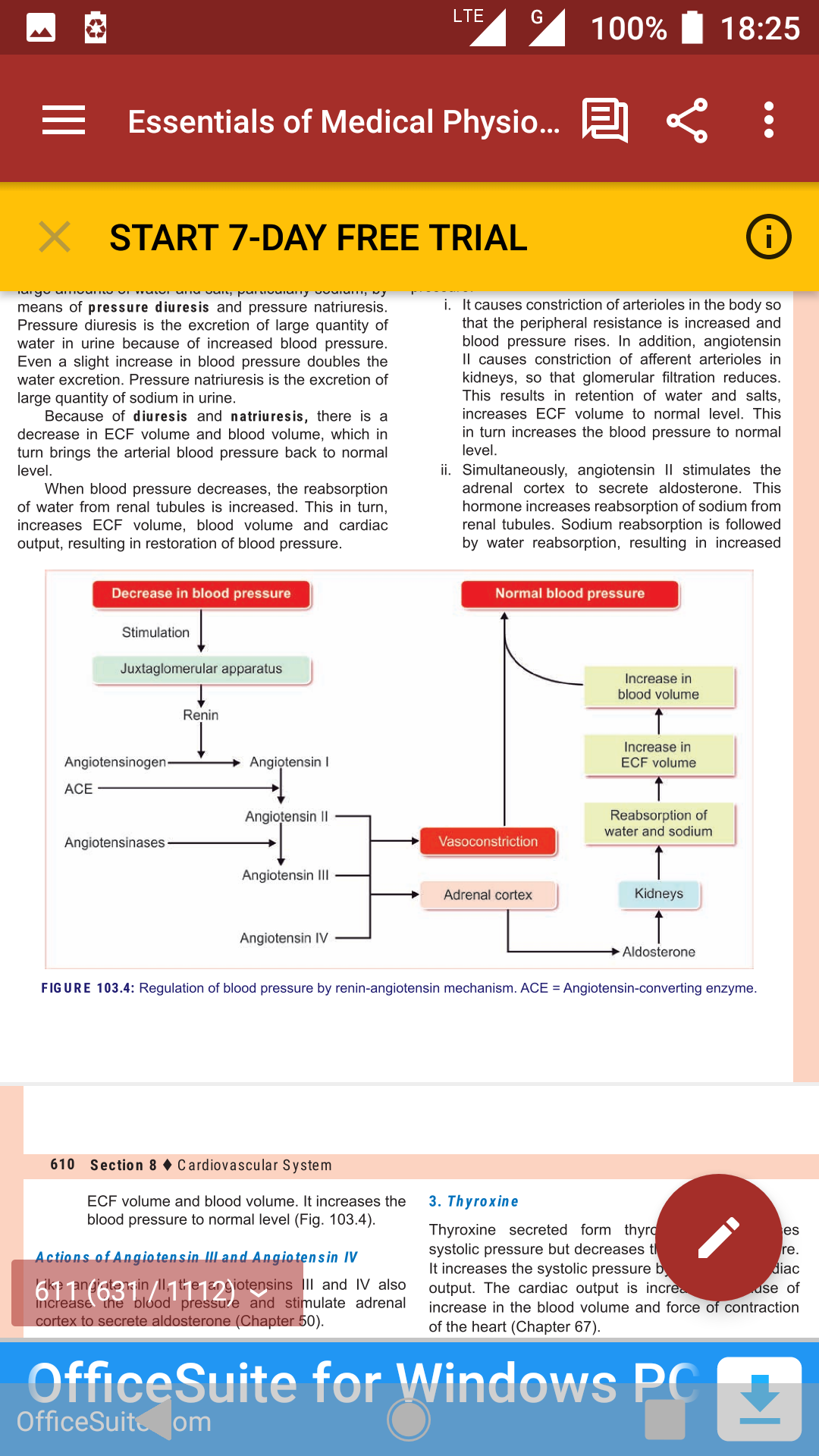
* When blood pressure decreases, the reabsorption of water from renal tubules is increased. This in turn, increases ECF volume, blood volume and cardiac output, resulting in restoration of blood pressure.

It is important to note that: Raising salt intake in the absence of impaired kidney function or excessive formation of ant natriuretic hormones usually does not increase arterial pressure much because the kidneys rapidly eliminate the excess salt and blood volume is hardly altered.



1. **THROUGH RENIN-ANGIOTENSIN MECHANISM**

Another powerful mechanism for controlling pressure Is the renin-angiotensin system (RAS).



Components of the Renin-Angiotensin System

1. Renin
2. Angiotensin

RENIN

Renin is a protein enzyme of 340 amino acids 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.

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 in the walls of the afferent arterioles immediately proximal to the glomeruli.

When the arterial pressure falls, intrinsic reactions in the kidneys themselves cause many of the prorenin molecules in the JG cells to split and release renin.

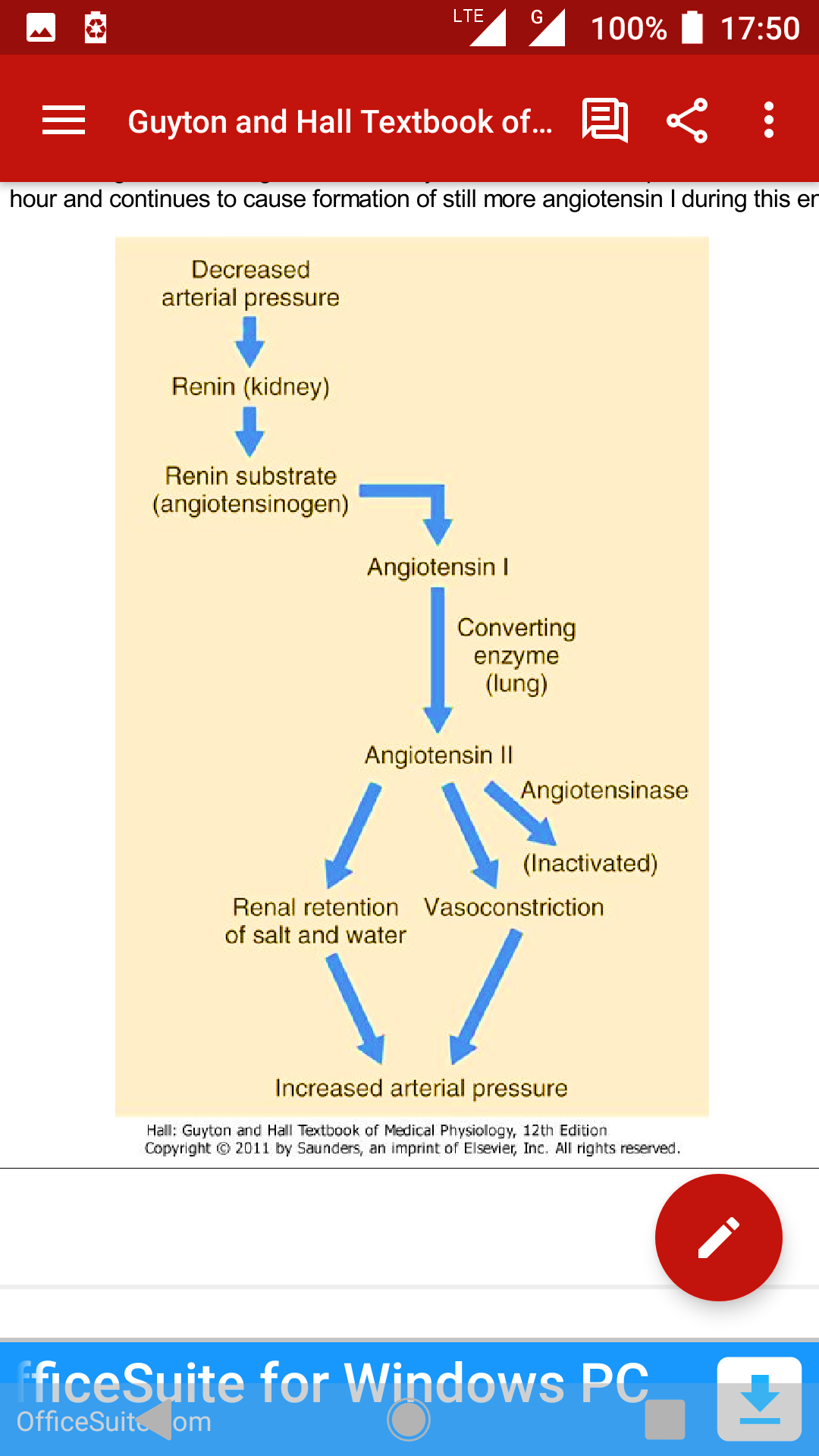
Most of the renin enters the renal blood and then passes out of the kidneys to circulate throughout the entire body. However, small amounts of the renin do remain in the local fluids of the kidney and initiate several intrarenal functions.

**Renin** itself is an enzyme, not a vasoactive substance. Renin acts enzymatically on another plasma protein, a globulin called **renin substrate** (**or angiotensinogen**).

ANGIOTENSIN

* **Angiotensinogen**: It is the alpha-2 globulin and has 452 amino acids. When renin is released into the blood, it acts enzymatically on angiotensinogen to release a 10- amino acids peptide, angiotensin-I
* **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.
* **Angiotensin II**: it is an 8-amino acids peptide. Angiotensin-I is converted to angiotensin II 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 (ACE) 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 also 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. The inactivated form is a 7-amino acid peptide, **angiotensin-111**, which is converted into **angiotensin-IV**, a 6-amino acid peptide.



During the persistence of angiotensin-II in the blood, angiotensin II has two principal effects that can **elevate** arterial pressure:

1. **Rapid vasoconstriction in many areas of the body: -**

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. 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.

NOTE: Renin angiotensin vasoconstrictor system requires about 20 minutes to become fully active. Therefore, it is somewhat slower to act for blood pressure control than are the nervous reflexes and the sympathetic norepinephrine-epinephrine system.

1. **Decreased excretion (or increased renal excretion) of both salt and water by the kidneys:**

This 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. Thus, whenever excess amounts of angiotensin II circulate in the blood, the entire long-term renal-body fluid mechanism for arterial pressure control automatically becomes set to a higher arterial pressure level than normal

Angiotensin II causes the kidneys to retain both salt and water in two major ways:

1. Angiotensin II acts directly on the kidneys to cause salt and water retention:

Angiotensin has several direct renal effects that make the kidneys retain salt and water.

* One major effect is to constrict the renal arterioles, thereby diminishing blood flow through the kidneys. The slow flow of blood reduces the pressure in the peritubular capillaries, which causes rapid reabsorption of fluid from the tubules.
* Another way is the direct actions of angiotensin-II on the tubular cells themselves to increase tubular reabsorption of sodium and water.

The total result of all these effects is significant, sometimes decreasing urine output to less than one fifth of normal.

1. Angiotensin II causes the adrenal glands to secrete aldosterone, and the aldosterone in turn increases salt and water reabsorption by the kidney tubules:

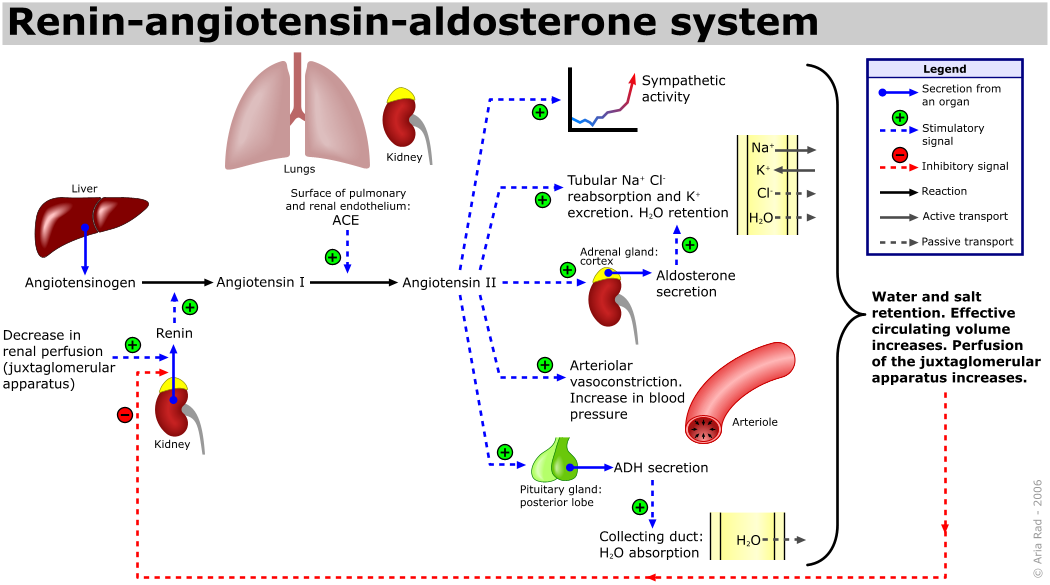
Angiotensin II is also one of the most powerful stimulators of aldosterone secretion by the adrenal glands. Therefore, when the renin-angiotensin system becomes activated, the rate of aldosterone secretion usually also increases; and an important subsequent function of aldosterone is to cause marked increase in sodium reabsorption by the kidney tubules, thus increasing the total body extracellular fluid sodium.

This increased sodium then causes water retention, increasing the extracellular fluid volume and leading secondarily to still more long-term elevation of the arterial pressure.

**Thus**, both the direct effect of angiotensin on the kidney and its effect acting through aldosterone are important in long-term arterial pressure control. However, research in our laboratory has suggested that the direct effect of angiotensin on the kidneys is perhaps three or more times as potent as the indirect effect acting through aldosterone-even though the indirect effect is the one most widely known.

Actions of Angiotensin III and Angiotensin IV

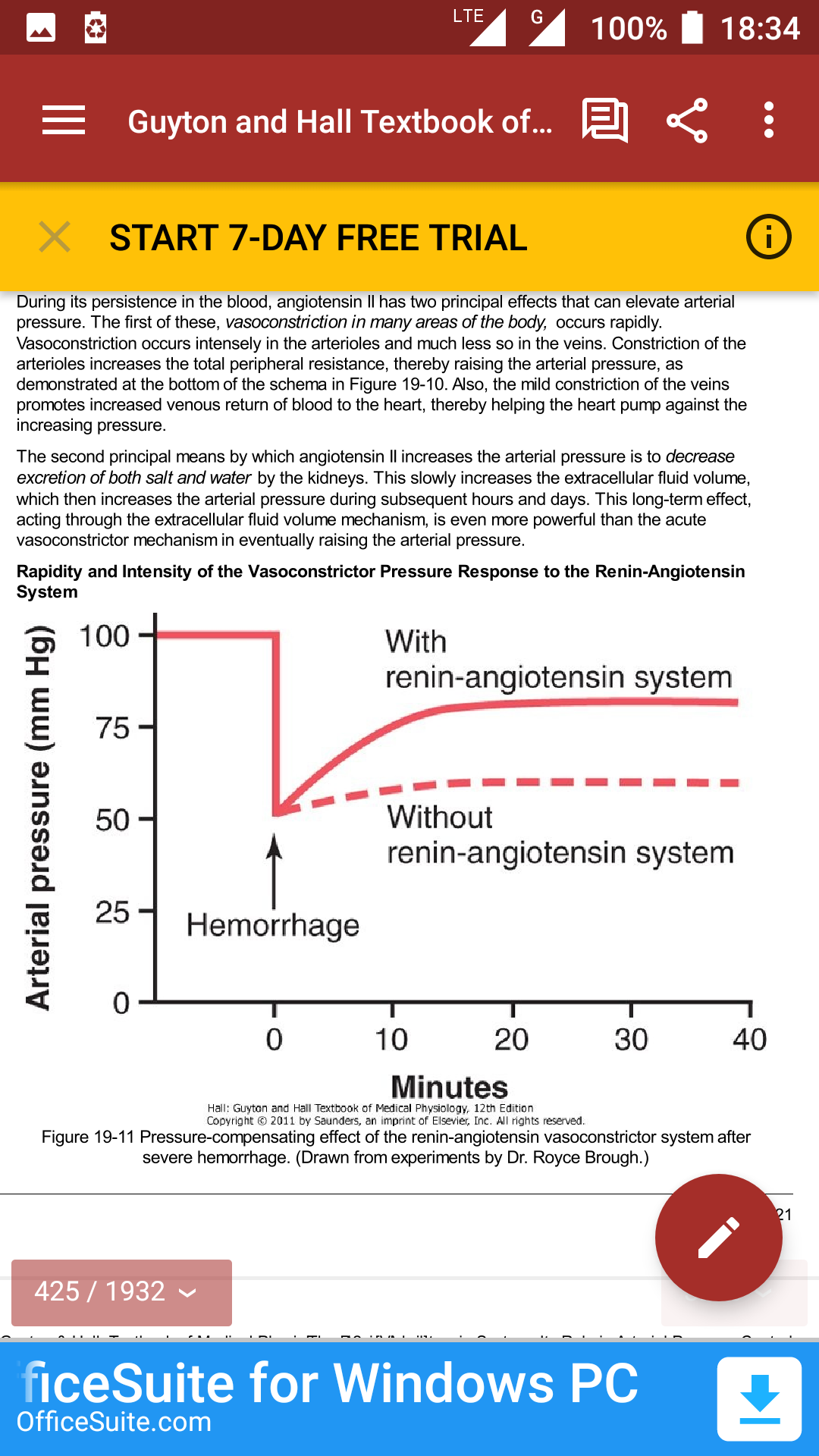
Like angiotensin II, the angiotensins III and IV also increase the blood pressure and stimulate adrenal cortex to secrete aldosterone.



APPLIED PHYSIOLOGY

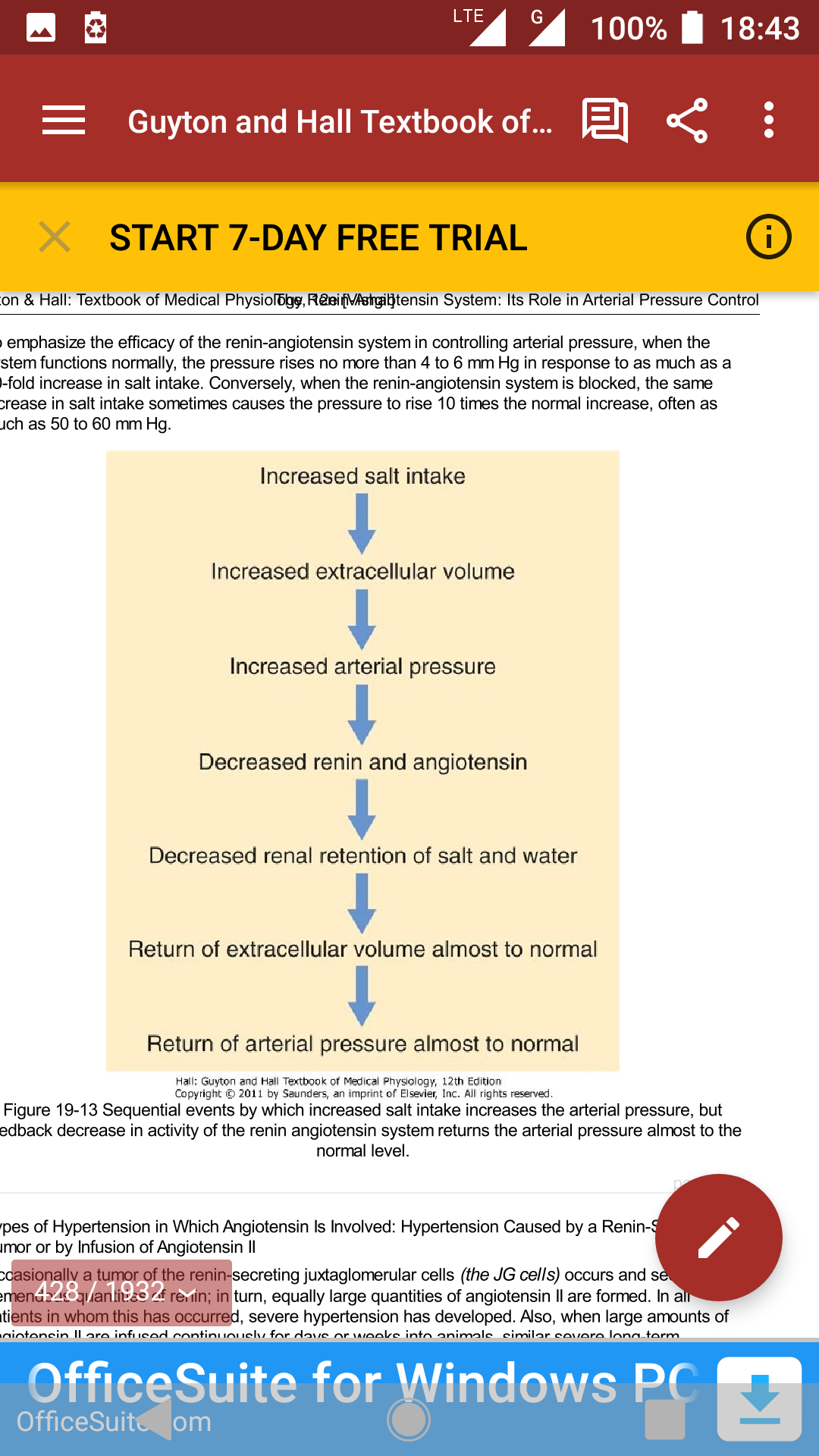
1. **Hemorrhage**:

The renin-angiotensin system is powerful enough to return the arterial pressure at least halfway back to normal within a few minutes after severe hemorrhage. Therefore, sometimes it can be of lifesaving service to the body, especially in circulatory shock.



1. **Role of the Renin-Angiotensin System in Maintaining a Normal Arterial Pressure Despite Large Variations in Salt Intake**

One of the most important functions of the renin-angiotensin system is to allow a person to eat either very small or very large amounts of salt without causing great changes in either extracellular fluid volume or arterial pressure.



Thus, the renin-angiotensin system is an automatic feedback mechanism that helps maintain the arterial pressure at or near the normal level even when salt intake is increased. Or, when salt intake is decreased below normal, exactly opposite effects take place.

To emphasize the efficacy of the renin-angiotensin system in controlling arterial pressure, when the system functions normally, the pressure rises no more than 4 to 6 mm Hg in response to as much as a 50-fold increase in salt intake. Conversely, when the renin-angiotensin system is blocked, the same increase in salt intake sometimes causes the pressure to rise 10 times the normal increase, often as much as 50 to 60 mm Hg.

1. **Hypertension Caused by a Renin-Secreting Tumor or by Infusion of Angiotensin II:**

Occasionally a tumor of the renin-secreting juxtaglomerular cells (the JG cells) occurs and secretes tremendous quantities of renin; in turn, equally large quantities of angiotensin II are formed. This results in development of severe hypertension.

1. **Chronic Hypertension (High Blood Pressure) Is Caused by Impaired Renal Fluid Excretion**

When a person is said to have chronic hypertension (or "high blood pressure"), it is meant that his or her mean arterial pressure is greater than the upper range of the accepted normal measure.

A mean arterial pressure greater than 110 mm Hg (normal is about 90 mm Hg) is considered to be hypertensive. (This level of mean pressure occurs when the diastolic blood pressure is greater than about 90 mm Hg and the systolic pressure is greater than about 135 mm Hg). In severe hypertension, the mean arterial pressure can rise to 150 to 170 mm Hg, with diastolic pressure as high as 130 mm Hg and systolic pressure occasionally as high as 250 mm Hg. Even moderate elevation of arterial pressure leads to shortened life expectancy. At severely high pressures (mean arterial pressures 50 percent or more above normal) a person can expect to live no more than a few more years unless appropriately treated.

Chronic Hypertension (High Blood Pressure) can be said to be Caused by Impaired Renal Fluid Excretion. Hypertension caused by excess accumulation of extracellular fluid in the body is called **“Volume-loading hypertension”**

The lethal effects of hypertension are caused mainly in three ways:

1. Excess workload on the heart leads to early heart failure and coronary heart disease, often causing death as a result of a heart attack.

2. The high pressure frequently damages a major blood vessel in the brain, followed by death of major portions of the brain; this is a cerebral infarct. Clinically it is called a "stroke." Depending on which part of the brain is involved, a stroke can cause paralysis, dementia, blindness, or multiple other serious brain disorders.

3. High pressure almost always causes injury in the kidneys, producing many areas of renal destruction and, eventually, kidney failure, uremia, and death.

Question five

Discuss the role of kidney in calcium homeostasis

CALCIUM HOMEOSTASIS

Extracellular fluid calcium ion concentration normally remains tightly controlled within a few percentage points of its normal level, 2.4 mEq/L.

ROLE OF KIDNEY IN CALCIUM HOMEOSTASIS

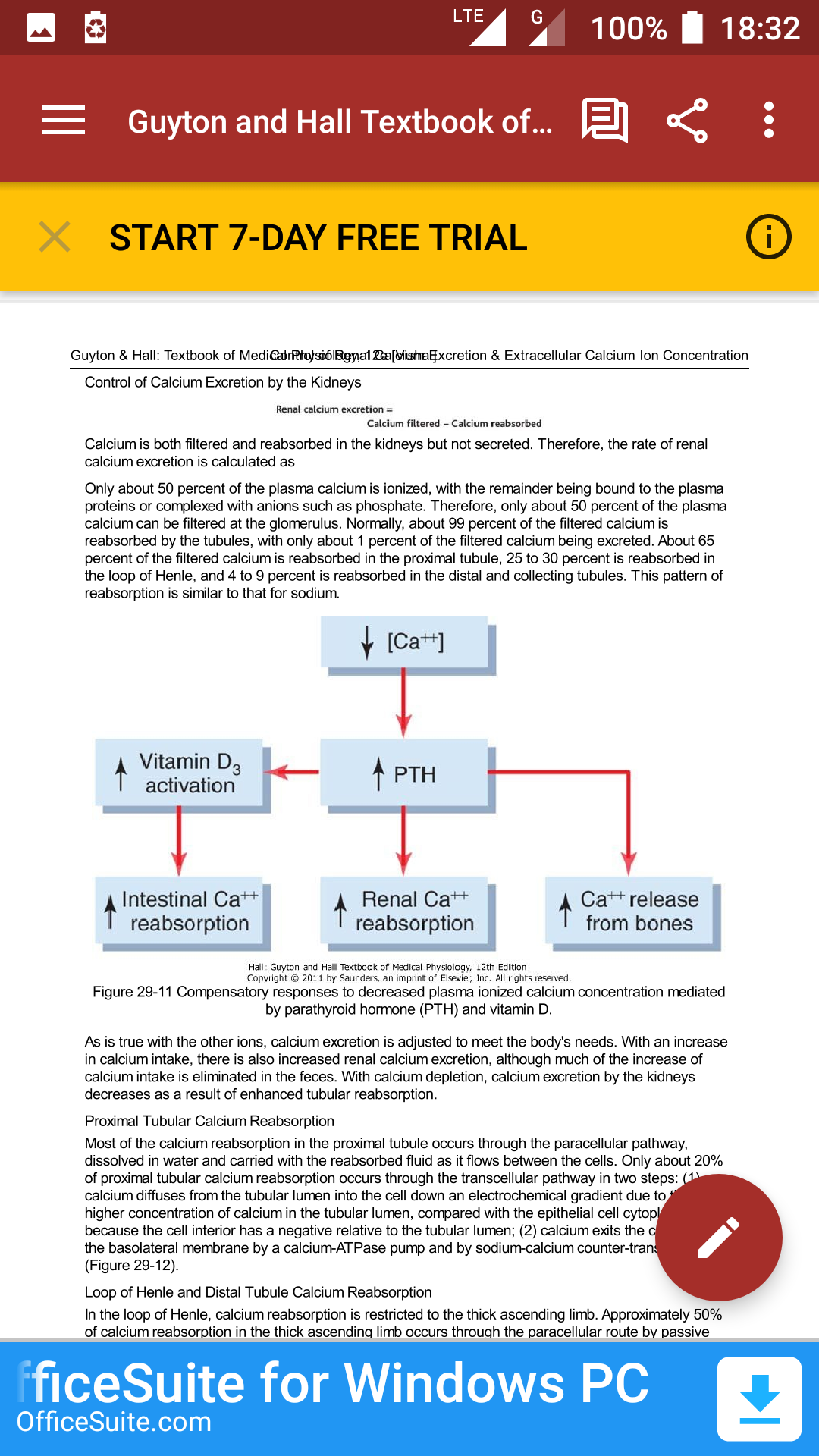
Calcium is both filtered and reabsorbed in the kidneys but not secreted. Therefore, the rate of renal calcium excretion is calculated thus:

Renal calcium excretion = calcium filtered – calcium reabsorbed

Only about 50 percent of the plasma calcium is ionized, with the remainder being bound to the plasma proteins or complexed with anions such as phosphate. Therefore, only about 50 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% of the filtered calcium is reabsorbed in the proximal tubule,
* 25 to 30% is reabsorbed in the loop of Henle, and
* 4 to 9% is reabsorbed in the distal and collecting tubules.



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.

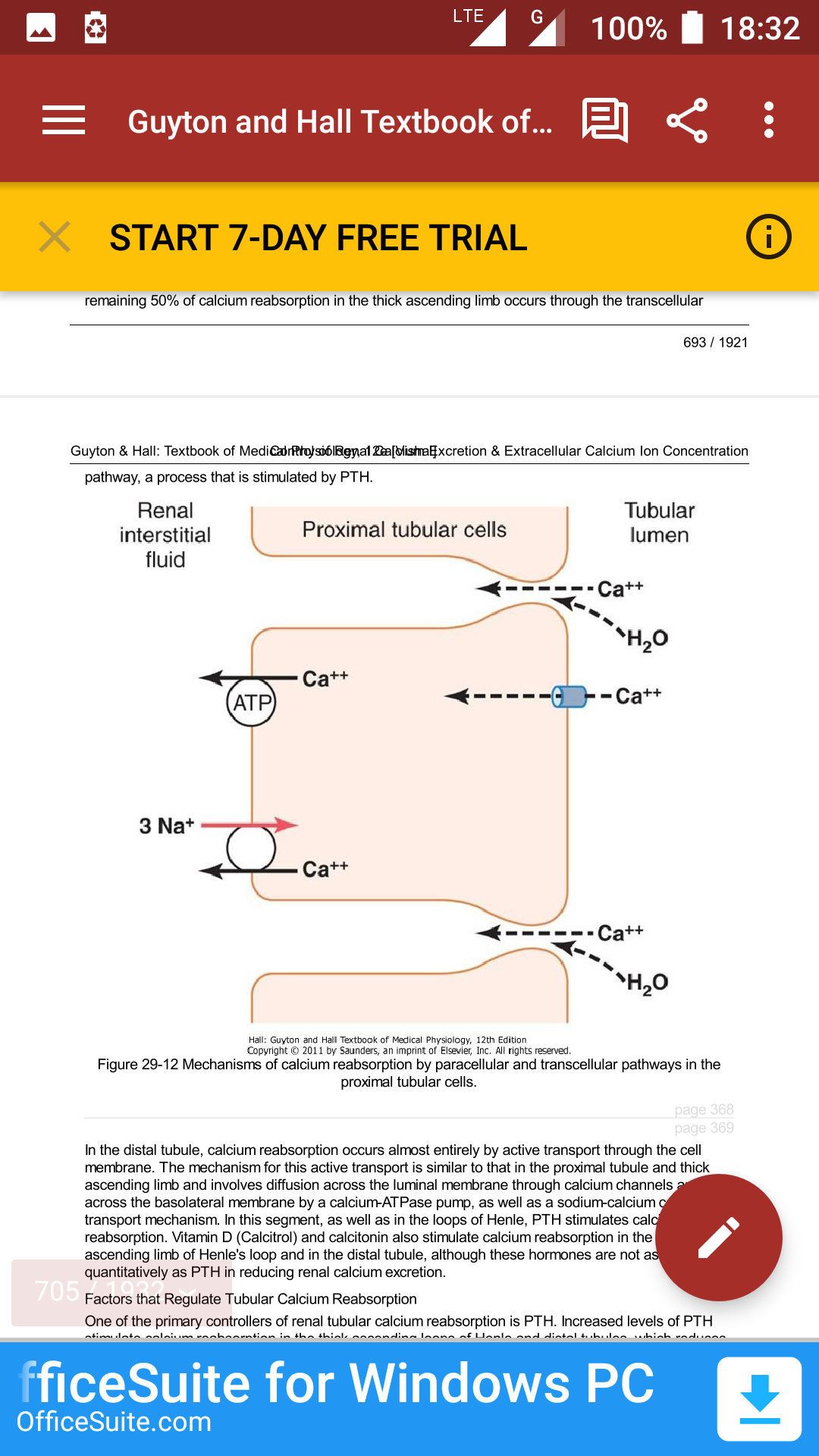
* Proximal Tubular Calcium Reabsorption

Most of the calcium reabsorption in the proximal tubule occurs through the **paracellular pathway**, 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:

Step 1: Calcium diffuses from the tubular lumen, through the calcium channels, 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 relative to the tubular lumen.

Step 2: Calcium exits the cell across the basolateral membrane by a calcium-ATPase pump and by sodium-calcium counter-transporter.

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* Loop of Henle 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 parathyroid hormone (PTH).

* Distal Convoluted Tubule Calcium Reabsorption

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. It involves:

1. Diffusion across the luminal membrane through calcium channels and
2. Exits across the basolateral membrane by a calcium-ATPase pump, as well as a sodium-calcium counter transport mechanism.

In the distal tubule, 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 acidosis and inhibited by metabolic alkalosis.

* Most of the effect of hydrogen ion concentration on calcium excretion results from changes in calcium reabsorption in the distal tubule.

APPLIED PHYSIOLOGY

1. **Hypocalcemia**

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 is characterized by spastic skeletal muscle contractions.

1. **Hypercalcemia**

Hypercalcemia (increased calcium concentration) depresses neuromuscular excitability and can lead to cardiac arrhythmias.