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COURSE: RENAL PHYSIOLOGY, BODY FLUID AND TEMPERATURE REGULATION.

ASSIGNMENT

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

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

Kidney plays an important role in glucose homeostasis, both in the post-absorptive and postprandial period. Kidney produces glucose by gluconeogenesis in the renal cortex and uses glucose for covering energy needs of the medulla. Kidney participates also to the reabsorption of filtered glucose in order the terminal urine was devoid of glucose, as long as blood glucose did not exceed 180mg/dL. Reabsorption of glucose is mediated by sodium-glucose cotransporters (SGLT1 and SGLT2) expressed in S1 and S3 segments of proximal tubule. SGLT2 is the main sodium-glucose cotransporter responsible for 90% of glucose reabsorption.

The regulation of endogenous production of glucose is determined by hormonal and neural factors. In the acute phase, glucoregulatory mechanisms involve insulin, glucagon and catecholamines and they can effect changes in plasma glucose levels in a matter of minutes. Insulin is able to suppress glucose release in both the kidney and liver by direct enzyme activation/deactivation and by reducing the availability of gluconeogenic substrates. Glucagon has no effect on the kidneys, but it stimulates glycogenolysis and gluconeogenesis in the liver. Catecholamines also have multiple acute actions. They can stimulate renal glucose release and glucagon secretion and inhibit insulin secretion.

The kidneys are involved in maintaining glucose homeostasis through three different mechanisms: **gluconeogenesis; glucose uptake from the blood for its own energy requests and reabsorption into the general circulation of glucose from glomerular filtrate in order to preserve energy.**

Renal gluconeogenesis

From the point of view of glucose utilization, the kidney is considered as 2 separate organs; the renal medulla is characterized mainly by glucose utilization and the renal cortex is responsible for glucose release. The separation of these activities represents the consequence of differences in the distribution of numerous enzymes along the nephron. 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. Moreover, the cells in the renal cortex have gluconeogenic enzymes and they can produce and release glucose into the circulation. However these cells cannot synthesize glycogen because they have little phosphorylating capacity.

Glycogenolysis

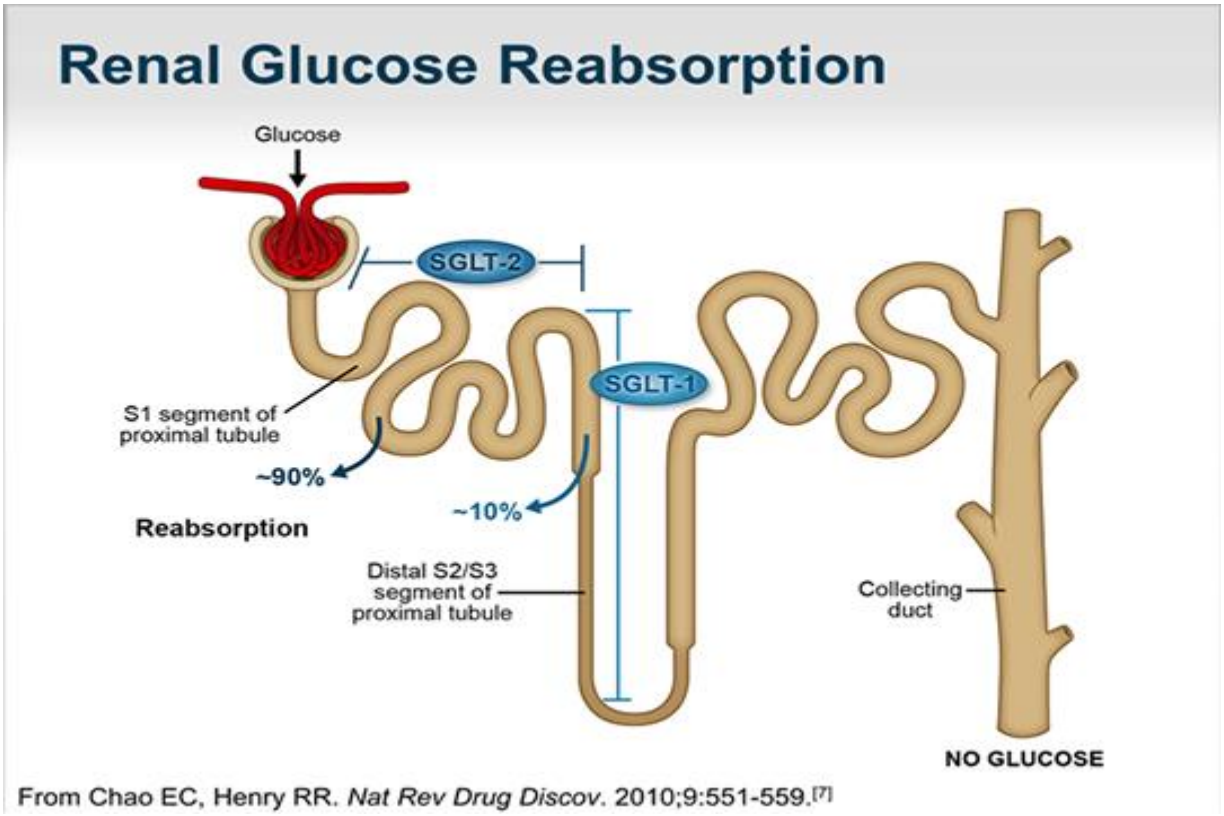
Glycogenolysis is the breakdown of glycogen to glucose-6-phosphate and a hydrolysis reaction (using glucose-6-phosphatase) in order to free glucose. The liver is the only organ that contains glucose-6-phosphatase. So, the cleavage of hepatic glycogen releases glucose, while the cleavage of glycogen from other sources can release only lactate. Lactate, that is generated via glycolysis, is often absorbed by other organs and helps regenerating glucose.

Glucose reabsorption

Apart from the important role in gluconeogenesis and the role of renal cortex in glucose uptake, 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. Nevertheless, there can be slight differences between the nephrons and the inaccurate nature of biological systems may potentially lead to the development of glucosuria when blood glucose is below TmG. Glucosuria may occur at lower plasma glucose levels in certain

conditions of hyperfiltration (eg. pregnancy), but as a consequence of hyperfiltration and not of significant hyperglycemia.



2. Discuss the process of micturition

Micturition or urination is the process of expelling urine from the bladder.. The excretory system in humans includes a pair of kidneys, two ureters, a urinary bladder and a urethra. The kidneys filter the urine and it is transported to the urinary bladder via the ureters where it is stored till its expulsion. The process of micturition is regulated by the nervous system and the muscles of the bladder and urethra. The urinary bladder can store around 350-400ml of urine before it expels it out.

Micturition is also known as voiding phase of bladder control and lasts for a short time. As the bladder becomes full, the stretch receptors increase their firing rate. This increase, the urge to urinate and causes micturition reflex. It sometimes even causes involuntary urination.

On average, a normal adult excretes 1 to 1.5 L of urine per day. Normal human urine is a light yellow fluid majorly consisting of 95 per cent water and 5 per cent solid wastes. It is slightly acidic with a pH close to 6.

Stages of Micturition

The urinary bladder has two distinct stages or phases:

- Resting or filling stage
- Voiding stage

Resting or Filling Stage

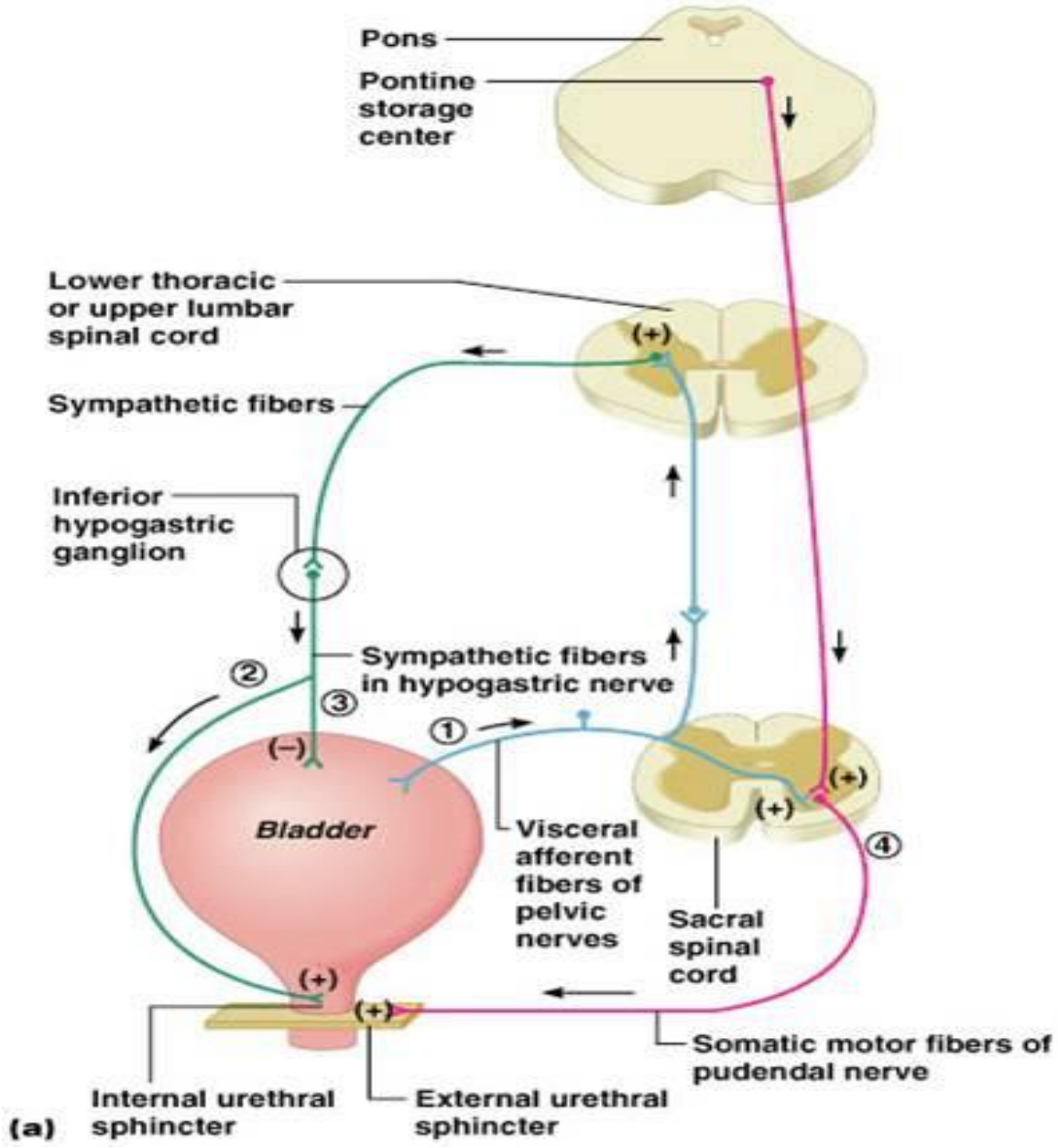
It is in this phase of the bladder that the urine is transported from the kidneys via the ureters into the bladder. The ureters are thin muscular tubes that arise from each of the kidneys and extend downwards where they enter the bladder obliquely.

The oblique placement of the ureters in the bladder wall serves a very important function. The opening of the ureter into the urinary bladder is not guarded by any sphincter or muscle. Therefore, this oblique nature of opening prevents the urine from re-entering the ureters. At the same time, the main muscle of the urinary bladder, the detrusor muscle, is relaxing allowing the bladder to distend and accommodate more urine.

Voiding Stage

During this stage, both the urinary bladder and the urethra come into play together. The detrusor muscle of the urinary bladder which was relaxing so far starts to contract once the bladder's storage capacity is reached.

The urethra is controlled by two sets of muscles: The internal and external urethral sphincters. The internal sphincter is a smooth muscle whereas the external one is skeletal. Both these sphincters are in a contracted state during the filling stage.



Micturition Reflex

At its most basic level, micturition is a simple reflex which is displayed by infants who are not toilet-trained.

When the volume of urine in the bladder reaches about 250ml, stretch receptors in the bladder walls are stimulated and excite sensory parasympathetic fibres which relay information to the sacral area of the spine. This information is integrated in the spine and relayed to two

different sets of neurones. Parasympathetic motor neurones are excited and act to contract the detrusor muscles in the bladder so that bladder pressure increases and the internal sphincter opens. At the same time, somatic motor neurones supplying the external sphincter via the pudendal nerve are inhibited, allowing the external sphincter to open and urine to flow out, assisted by gravity.

Control of micturition

Children and adults have considerable control over when and where they pass urine. They can also increase or decrease the rate of flow and even stop and start again, so micturition is clearly more than just a simple reflex. This control is learnt in infancy and involves other sensory fibres in the bladder wall. These fibres convey information on the degree of bladder fullness via the spine to the higher centres of the brain, the thalamus and cerebral cortex. This causes us to become aware that we need to pass urine and of the urgency of the situation.

These links between the spine and cerebral cortex are not established until about two years of age and it is suggested that toilet-training is therefore not physiologically possible until that time.

The brain is able to override the micturition reflex by inhibiting the parasympathetic motor nerve fibres to the bladder and reinforcing contraction of the external sphincter. The internal sphincter will not open until the external sphincter does.

The increase in bladder volume increases stretch receptor and nerve activity, making the sensation of pressure more acute. When it is convenient, the brain centres remove the inhibition and permit micturition under our conscious control. When the bladder contains about 500ml, pressure may force open the internal sphincter; this in turn forces open the external sphincter and urination occurs whether it is convenient or not.

We can increase the rate of urine flow by contraction of the abdominal muscles and by the performance of Valsalva's manoeuvre (forced expiration against a closed glottis). Contraction of the strong pelvic floor muscles can stop urine in mid-flow. The sound of running water also

encourages micturition but some people cannot urinate in the presence of others, no matter how great their need. After micturition, less than 10ml of urine remains in the bladder and the cycle begins again.

Problems Associated With Micturition

There are several factors which affect the process of micturition. Some of these can be due to physical trauma or disease; others are psychological in nature. Following are a few disorders that affect micturition:

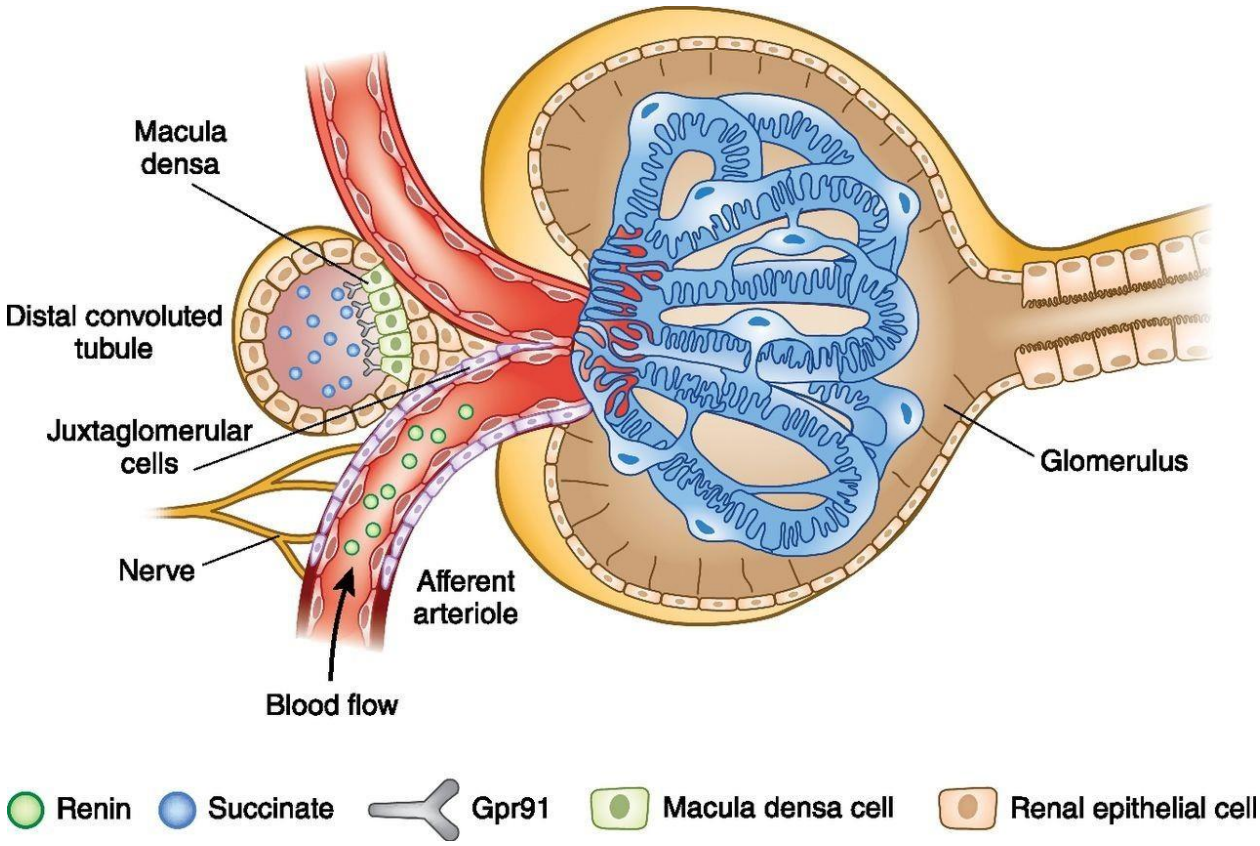
- **Detrusor Instability –** This is a condition where the detrusor muscle contracts without any apparent reason. This muscle is responsible for contracting the bladder and help with the micturition process. As a result, detrusor instability results in urinary incontinence.
- **Urinary Retention –** This condition is characterized by the inability to empty the bladder completely. The onset may be gradual or sudden. The causes can range from a blockage in the urethra, nerve problems and weak bladder muscles.
- **Spinal Cord Trauma –** Injuries to the spinal cord, specifically the tenth thoracic vertebra (T10) can cause the bladder to be overactive or cause urinary incontinence.

3. Discuss the juxtaglomerular apparatus.

The **juxtaglomerular apparatus** (also known as the **juxtaglomerular complex**) is a structure in the kidney that regulates the function of each nephron, the functional units of the kidney. The juxtaglomerular apparatus is named because it is next to (juxta) the glomerulus.

The juxtaglomerular apparatus consists of three types of cells:

1. The macula densa, a part of the distal convoluted tubule of the same nephron.
2. Juxtaglomerular cells, (also known as granular cells) which secrete renin.
3. Extraglomerular mesangial 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.

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.

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.

The two main hormones secreted by the juxtaglomerular apparatus are;

1. Renin
2. Prostaglandins

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 the kidney in the regulation of blood pressure.**

The kidney plays a central role in the regulation of arterial blood pressure. A large body of experimental and physiological evidence indicates that renal control of extracellular volume and renal perfusion pressure are closely involved in maintaining the arterial circulation and blood pressure. Renal artery perfusion pressure directly regulates sodium excretion-a process known as pressure natriuresis-and influences the activity of various vasoactive systems such as the renin-angiotensin-aldosterone system. As a result, many researchers argue that identifying any marked rise in blood pressure requires resetting of the relationship between arterial blood pressure and urinary sodium excretion, which can occur by an array of systemic or local mechanisms. Almost all of the monogenic forms of hypertension affect sites in the kidney associated with sodium handling and transport.

The kidneys regulate blood pressure using three different mechanisms:

Three mechanisms of Renal Regulation

Pressure Diuresis

As arteriolar blood pressure increases, so flow through the kidneys also increases. This increases filtration rate. This increases urinary output.

Pressure Natriuresis

If renal perfusion pressure is increased then sodium excretion increases (I.e. sodium excretion increases when blood pressure increases). If more sodium is excreted less water is reabsorbed therefore the ECF volume decreases and blood pressure decreases.

The actual mechanism is not clear but it is thought to involve a direct effect of the pressure on the renal interstitium.

Renin-Angiotensin-Aldosterone System

Specialized cells in the distal tubule called the macula densa sense the concentration of sodium and chloride.

If blood pressure falls there is a reduction in concentration of sodium and chloride in the distal tubule which is sensed by the macula densa.

The macula densa releases prostaglandins which act on the juxtaglomerular apparatus which releases renin into the bloodstream.

The drop in blood pressure is also detected by baroreceptors in the aortic arch, carotid sinus and the afferent renal arteriole which stimulates renin release by the juxtaglomerular apparatus.

Renin cleaves angiotensinogen into angiotensin 1 which in turn is cleaved by **Angiotensin Converting Enzyme** (ACE) into angiotensin 2.

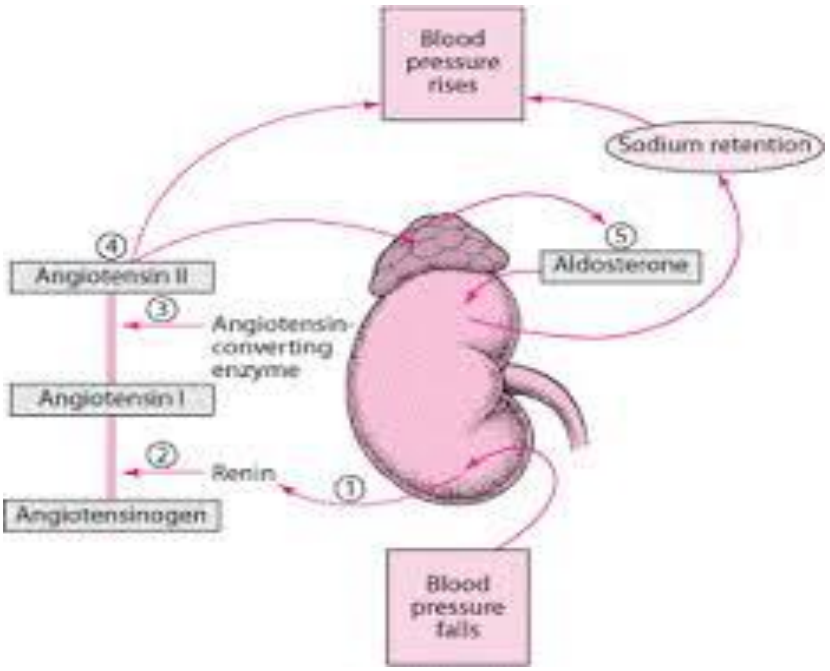
Angiotensin 2 is a potent vasoconstrictor and also stimulates the adrenal cortex to release aldosterone.

Aldosterone acts on the distal tubules and collecting ducts in the kidney causing retention of sodium and water.

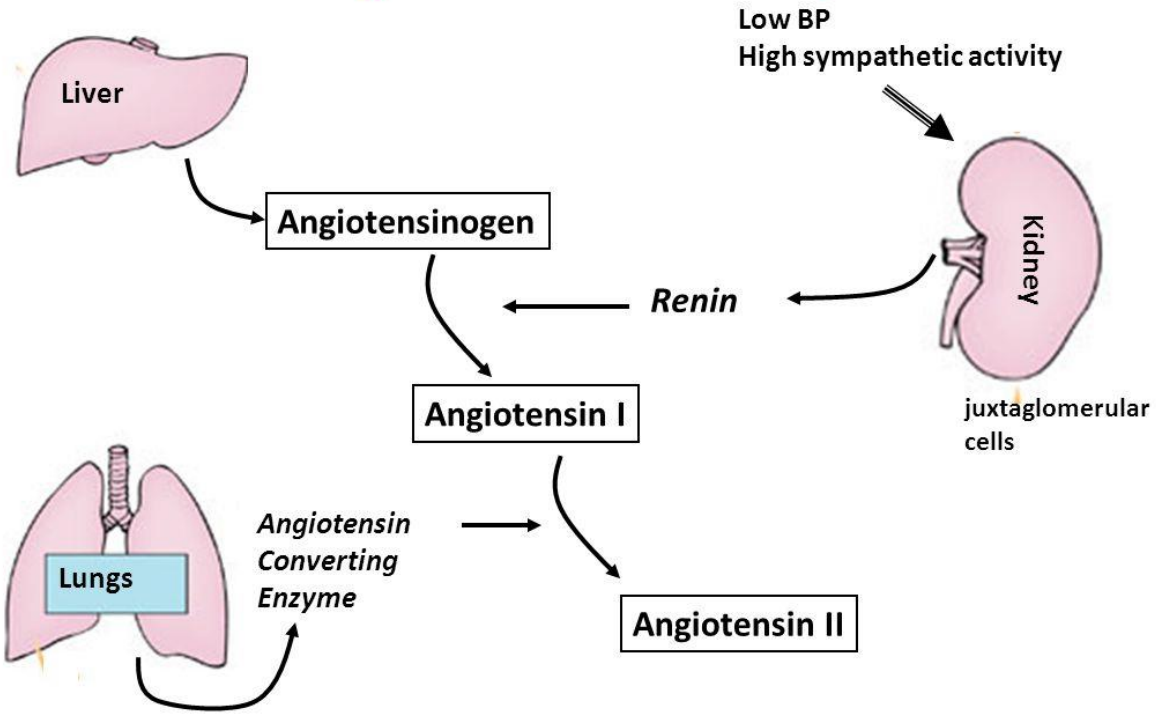
Blood pressure increases.

Regulation of Renal Blood Flow

It is essential that renal blood flow is maintained to ensure that adequate filtration of toxins from the blood takes place. Changes in pressure affect renal blood flow. Important auto-regulatory processes are responsible for this.



Renal regulation of blood pressure



5. Discuss the role of the kidney in calcium homeostasis

The maintenance of calcium homeostasis is very important because calcium is the main component of bony skeleton and serves as the intracellular and extracellular messenger in numerous essential cellular events such as neuronal network, immune response, muscle contraction, and hormone secretion. Total body calcium in the adult human is about 1-2 kg and 99% of total calcium exists in bone. Even though only less than 1% of body calcium is in the extracellular space, maintaining the extracellular calcium concentration within a narrow range (8.5-10.5 mg/dL) is very important for calcium homeostasis. Approximately 40% of plasma calcium is protein-bound and 10% of calcium is in a complex with anions like phosphate, citrate, and sulfate etc. Only half of plasma calcium is in its free form (ionized form, iCa^{2+}) and physiologically important. The ionized calcium is tightly regulated by hormones like parathyroid hormone (PTH), 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), calcitonin, and calcium itself. The kidney, intestine, and bone are the main target organs of these regulators, and the kidney plays a key role in the fine regulation of calcium excretion.

- The regulation of ECF calcium levels is complex and involves the interaction of multiple endocrine hormones acting on multiple organ systems). The unique aspect of calcium is that bone represents a large store of the ion that can be mobilized to maintain ECF calcium levels. However, the bone calcium reservoir is not inexhaustible and over the long-term calcium intake must be balanced with calcium excretion. Regulated calcium excretion occurs both in the intestines and kidneys. Here we focus on renal calcium excretion which is largely regulated by its rate of tubular resorption.

Calcium Transport

- **Overview**

It should be noted that protein-bound calcium cannot be filtered through the glomerular barrier and thus is not subject to renal regulation. Consequently, only the unbound ionic ECF calcium, representing 60% of

the total, is subject to renal regulation. Calcium resorption occurs in multiple segments of the nephron via distinct resorptive mechanisms.

- **Proximal Tubule and Thick Ascending Loop of Henle**
  - Roughly 67% of calcium is resorbed in the proximal tubule while 25% is resorbed in the thick ascending Henle. Calcium resorption in these early segments occurs largely via a *paracellular* route and is dependent on the large amounts of sodium resorption performed. When sodium resorption is inhibited, either by the action of diuretics or ECF volume expansion, calcium resorption also declines and its urinary loss increases.
  - The driving force for calcium resorption in the proximal tubule is likely the fact that the ion becomes concentrated as large volumes of water are resorbed in this segment. This is also the case in the thick Henle but in addition the thick Henle carries a large positive luminal potential that adds to the driving force for paracellular calcium resorption.

- **Early Distal Tubule**
  - The early distal tubule is responsible for resorbing the remaining 8% of filtered calcium; however, as discussed below this segment represents the most important locus for regulation of calcium excretion. Unlike the proximal tubule and thick Henle, resorption of calcium in the early distal tubule is independent of sodium. Here, luminal calcium resorption appears to occur through a calcium channel. The resorptive electrochemical gradient for calcium is generated by a basolateral calcium-ATPase.

Regulation

- Renal calcium resorption is enhanced by all three calcium-modulating hormones, Parathyroid Hormone (PTH), Vitamin D, and Calcitonin; however, the most important hormone is PTH. As discussed in parathyroid hormone physiology, PTH levels are modulated by both blood calcium and phosphate levels. All things being equal, PTH levels rise when blood calcium levels fall whereas PTH levels fall when blood calcium levels rise. The capacity of PTH to enhance renal calcium resorption appears to be by stimulating the basolateral calcium-ATPase in the early distal tubule. Taken together then, the relationship between blood calcium levels, PTH, and renal sodium excretion represent a negative feedback control circuit that

maintains relatively stable levels of ECF calcium concentration over the long term.