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ASSIGNMENT

1. DISCUSS THE ROLE OF KIDNEY IN GLUCOSE HEMOSTASIS
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

ANSWERS

1.THE ROLE OF KIDNEY IN GLUCOSE HOMEOSTASIS

The plasma glucose concentration is determined by the amount of glucose synthesized, and the one 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 . Other substrates such as free fatty acids (FFAs), glycerol, lactate and ketone bodies have greater daily fluctuations. This can be explained by the need of the body to protect himself against hyper- and hypoglycaemia. Hyperglycaemia is associated with both chronic effects (such as nephropathy, retinopathy, neuropathy and premature atherosclerosis) and also acute complications (including diabetic ketoacidosis that are associated with higher morbidity and mortality). Hypoglycaemia is also harmful because it can cause neurological events (including coma, seizures)etc.

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 etc

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 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.

After a 16-h overnight fast, approximately 10 µmol ⁄ (kg /min) of glucose is released into the circulation. 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, 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 kidney. Lactate represents the predominant gluconeogenic precursor in both organs, but regarding the aminoacids, the kidney prefers to use glutamine. Insulin can suppress glucose release in both organs with almost comparable efficacy .Renal gluconeogenesis can increase by approximately twofold and it can represent ~60% of endogenous glucose production in the postprandial state .This mechanism is believed to facilitate the repletion of glycogen stocks in the liver.A new concept of hepatorenal glucose reciprocity emerged from the differences observed in regulation and interchange between renal and hepatic glucose release .This concept refers to the facts that a pathological or physiological reduction in glucose release by kidney or liver determines a compensatory increase in glucose release of the other one (liver or kidney) in order to avoid hypoglycaemia. This situation occurs in the anhepatic phase during liver transplantation, prolonged fasting etc.

**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. 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 :** 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 m2 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 .

In a given day, the kidneys can produce, via gluconeogenesis, 15–55g glucose and it can metabolize 25–35g glucose. Regarding the glucose metabolic pathways, it is obvious that renal reabsorption represents the main mechanism by which the kidney is involved in glucose homeostasis. Therefore, the change in tubular glucose reabsorption may have a considerable impact on glucose homeostasis .

**Renal glucose transporters**

Glucose is a polar compound with positive and negative charged areas; therefore it is soluble in water. Its transport into and across cells is dependent on two specialized carrier protein families: the GLUTs (facilitated glucose transporters) and the SGLTs (sodium-coupled glucose cotransporters). These transporters are responsible for glucose passage and reabsorption in several tissue types, including the proximal renal tubule, blood-brain barrier, small intestine . GLUTs are responsible for the passive transport of glucose across cell membranes, in order to equilibrate its concentrations across a membrane. SGLTs are involved in active transport of glucose against a concentration gradient by means of sodium-glucose cotransport . There are six members of the SGLT family indicated in [Table 1](https://www.intechopen.com/books/treatment-of-type-2-diabetes/the-role-of-the-kidney-in-glucose-homeostasis#T1).

| **Co-transporter** | **Substrate** | **Tissue distribution** |
| --- | --- | --- |
| SGLT1 | Glucose, galactose | Intestine, kidney, heart, trachea, brain, testis, prostate |
| SGLT2 | Glucose | Kidney, brain, liver, muscle, heart |
| SGLT4 | Glucose, mannose | Intestine, kidney, uterus, pancreas, liver, brain, lung, trachea |
| SGLT5 | Unknown | Kidney |
| SGLT6 | Glucose, myoinositol | Brain, kidney, intestine |
| SMIT1 | Glucose, myoinositol | Brain, heart, lung, kidney |

SGLT2 is considered the most important because, based on animal studies, it is responsible for the reabsorption of 90% of the glucose filtered at the glomerulus . The other 10% of glucose reabsorbed in the proximal tubule is ensured by SGLT1. Of the family of GLUT proteins expressed in the kidneys, GLUT2 is the major transporter and it releases into circulation the glucose reabsorbed by SGLTs in the proximal tubular cells .The renal glucose transport was investigated by analyzing the gene mutations within SGLT family. These can lead to several inherited diseases presenting renal glucosuria that include familial renal glucosuria (FRG) and glucose-galactose malabsorption (GGM).

2. THE PROCESS OF MICTURITION

## Micturition or urination is the process of expelling urine from the bladder.

## Stages of Micturition

## The urinary bladder has two distinct stages

1.Resting or filling stage

2.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](https://www.toppr.com/guides/maths/relations-and-functions/functions/). The opening of the ureter into the urinary bladder is not guarded by any sphincter or muscle. Therefore, this oblique [nature](https://www.toppr.com/guides/business-studies/business-services/nature-and-types-of-services/) 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](https://www.toppr.com/guides/biology/locomotion-and-movement/skeletal-system/). Both these sphincters are in a contracted state during the filling stage.

### 3. JUXTAGLOMERULAR APPARATUS

**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 cells, derived from smooth muscle cells, of the afferent arteriole secrete renin when blood pressure in the arteriole falls. Renin increases blood pressure via the renin-angiotensin-aldosterone system .

4. THE ROLE OF KIDNEY IN REGULATION OF BLOOD PRESSURE

An important part of normal physiological function is that arterial pressure remains within relatively narrow limits. A lower than normal pressure produces disorientation and acute intolerance to upright posture. A higher than normal pressure is much insidious. Hypertension over the long term causes little acute discomfort while increasing mortality and morbidity in a statistical fashion. Typical sequelae include obstruction or rupture of major blood vessels with frequent involvement of the brain, heart, and kidneys. Genetic influences and physiological mechanisms combine to minimize fluctuations in arterial pressure. The importance of genetic influences is underscored by the observation that hypertension is likely to occur in the children of hypertensive parents and strains of ani-mals have been developed by repetitive inbreeding that become predictably hypertensive, while other strains have been inbred to remain, just as predictably, normotensive. Such demonstrations of the heritability of blood pressure have added much to understanding of blood pressure control in general, but they have not helped much in settling the question of exactly which physiological mechanisms are involved. All of the organs of the body must have adequate perfusion and teleologically all might be suspected of having some direct or indirect involvement in the control of blood pressure. The brain is most conspicuous, since normal cerebral function is lost when arterial pressure in the brain is insufficient for only a few moments. Further, hydrostatic forces reduce pressure as blood travels toward the head during upright posture and this puts the brain in special jeopardy. In response to these needs, it appears that the autonomic nervous system has evolved in such a way that a rapid and forceful neural response will occur if cerebral perfusion is threatened. The baroreceptor reflexes tend to preserve pressure and flow in the brain and heart at the expense of other tissues. This is not likely to be a suitable method of blood pressure control over prolonged periods. Consider the case of upright posture. In the absence of the baroreceptor reflexes, arterial pre-pressure decrease is secondary to a fall in cardiac output. The fall in cardiac output, in turn, results from gravitational translocation of blood to the lower torso with concomitant impairment of venous return. The baroreceptor reflexes do not provide full hemodynamic compensation. Reflex vasoconstriction in organs other than the heart and brain tends to maintain the systemic arterial pressure and cerebral perfusion; but, vasoconstriction per se will further depress, rather than enhance, many regional flows and cardiac output in general. The short-term merits of such a response would undoubtedly become liabilities over prolonged periods of time. In considering the

special metabolic requirements of all of the tissues of the body, the regulation of arterial pressure is tightly linked to the overall maintenance of adequate blood flow. Adequate flow, in turn, depends on some fundamental aspects of cardiovascular function: the pumping ability of the heart, vascular (and especially venous) tone, and the adequacy of body fluid volumes. With respect to the last factor, the volume and com-position of body fluids involve salt and water balance and the kidney. Therefore, as the kidney participates in the control of arterial pressure, its most important role may be in stabilizing cardiovascular performance over the long term rather than in responding to acute disturbances.

5.THE ROLE OF KIDNEY IN CALCIUM HOMEOSTASIS

The **kidney** is critcally important in calcium homeostasis. Under normal blood calcium concentrations, almost all of the calcium that enters glomerular filtrate is reabsorbed from the tubular system back into blood, which preserves blood calcium levels. If tubular reabsorption of calcium decreases, calcium is lost by excretion into urine. The kidney has been known as the central organ for calcium homeostasis through fine regulation of renal calcium excretion. For the past decade, there has been big progress in the understanding of the roles of the kidney in calcium homeostasis. The identification of calcium transport proteins and the molecular approach to the regulatory mechanisms achieved a major contribution to this progress. TRPV5, TRPV6, calbindin-D28K, NCX1, and PMCA1b have been identified as the main calcium transport proteins in the distal nephron. PTH, vitamin D, i[Ca2+], CaSR, and other various conditions control renal calcium excretion through the regulation of these transport proteins. Klotho and FGF23 emerged as new players in calcium metabolism in the kidney.