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COURSE TITLE: RENAL PHYSIOLOGY, BODY FLUIDS AND TEMPERATURE REGULATION.

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ASSIGNMENT TITLE: RENAL PHYSIOLOGY FOR MBBS STUDENTS.

1. Discuss the role of kidney in glucose homeostasis.

**Answer:** The concentration of glucose in plasma is held within narrow limits (4–10 mmol/l), primarily to ensure fuel supply to the brain. Kidneys play a role in glucose homeostasis in the body by ensuring that glucose is not lost in the urine. Three membrane proteins are responsible for glucose reabsorption from the glomerular filtrate in the proximal tubule: sodium−glucose cotransporters SGLT1 and SGLT2, in the apical membrane, and GLUT2, a uniporter in the basolateral membrane.

In both S1/S2 and S3 segments of the proximal tubule, the first stage is glucose transport across the apical membrane by SGLT1 and SGLT2 via reabsorption. This leads to glucose accumulation within the epithelium, modulated to some extent by intracellular metabolism. The glucose concentration gradient between the cell and plasma in turn drives the second stage: net passive exit of glucose through the basolateral membrane, towards the plasma, via GLUT2. The basolateral Na+/K+ pump (which extrudes three sodium ions for every two potassium ions entering the cell) maintains the sodium gradient across the apical membrane by pumping sodium out of the cell, towards plasma. Inhibition of the Na+/K+ pump by cardiac glycosides blocks the pumping of sodium out of the cell, with the concomitant rise in intracellular sodium concentration. The elimination of the sodium gradient across the apical membrane results in the loss of sodium–glucose cotransport across the apical membrane. Thus, the two-stage process, together with the absorption of glomerular fluid, accounts for the complete absorption of glucose by the time the filtrate reaches the end of the proximal tubule.

1. Discuss the process of micturition.

**Answer**: Micturition is the process of discharging urine from the urinary bladder. It is how urine is expelled from the body.

The bladder can hold about 350-400ml of urine. Micturition has two stages:

1. Filling stage
2. Voiding stage

**THE PROCESS**

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) while 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.

1. Explain the juxtaglomerular apparatus.

**Answer:** 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 lies between the glomerulus and the distal convoluted tubule of the same nephron. This location is critical to its function in regulating renal blood flow and thus the glomerular filtration rate (GFR). The main function of the juxtaglomerular apparatus is to regulate blood pressure and the filtration rate of the glomerulus.

The juxtaglomerular apparatus consists of three cell types:

i. the macula densa cells

ii. the juxtaglomerular cells

iii. the extraglomerular mesangial cells.

 The juxtaglomerular apparatus serves as an intrarenal baroreceptor that is composed of four basic elements:

1. the terminal portion of the afferent [arteriole](https://www.sciencedirect.com/topics/medicine-and-dentistry/arteriole),
2. the [macula densa](https://www.sciencedirect.com/topics/medicine-and-dentistry/macula-densa) (a segment of the distal tubule)
3. the extraglomerular mesangial region, and
4. the efferent arteriole at the [glomerulus](https://www.sciencedirect.com/topics/medicine-and-dentistry/glomerulus)

 Because of its location in the [nephron](https://www.sciencedirect.com/topics/medicine-and-dentistry/nephron), it is highly sensitive to changes in volume as induced by various [diuretic](https://www.sciencedirect.com/topics/medicine-and-dentistry/diuretic-agent) classes, and thus it is sensitive to changes in [kidney perfusion](https://www.sciencedirect.com/topics/medicine-and-dentistry/kidney-perfusion) pressure. The juxtaglomerular apparatus is also known to be adrenergically innervated, and has [β-1 adrenoreceptors](https://www.sciencedirect.com/topics/medicine-and-dentistry/beta-1-adrenergic-receptor).

1. Discuss the role of kidney in regulation of blood pressure.

**Answer:** The kidney plays a special 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. It is therefore argued 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.

Also Guytonarticulated the argument for the central role for the kidney in BP control, and the relationship between alterations in systemic blood pressure and changes in renal sodium excretion is well documented. For example, an elevation in perfusion pressure in the renal artery results in a rapid increase in sodium and water excretion by the kidney, so-called “pressure natriuresis.” Based on such observations, Guyton et al suggested that whenever arterial pressure is elevated, activation of this pressure-natriuresis mechanism will cause sufficient excretion of sodium and water to return systemic pressures to normal. They further hypothesized that the substantial capacity for sodium excretion by the kidney provides a compensatory system of virtually infinite gain to oppose processes, including increases in peripheral vascular resistance, which would tend to increase blood pressure. It follows then that defects in renal excretory function would, therefore, be a prerequisite for sustaining a chronic increase in intra-arterial pressure.

1. Discuss the role of kidney in calcium homeostasis.

**Answer:** Maintaining constant concentrations of calcium in blood requires frequent adjustments, which can be described as fluxes of calcium between blood and other body compartments. The kidney is critically important in this homeostasis.

Plasma calcium concentration is maintained within a narrow range (8.5-10.5 mg/dL) by the coordinated action of parathyroid hormone (PTH), 1,25(OH)2D3, calcitonin, and ionized calcium (iCa2+) itself. The kidney plays a key role in this process by the fine regulation of calcium excretion. More than 95% of filtered calcium is reabsorbed along the renal tubules. In the proximal tubules, 60% of filtered calcium is reabsorbed by passive mechanisms. In the thick ascending limb, 15% of calcium is reabsorbed by paracellular diffusion through paracellin-1 (claudin-16). The calcium sensing receptor (CaSR) in the basolateral membrane of the thick ascending limb senses the change in iCa2+ and inhibits calcium reabsorption independent to PTH and 1,25(OH)2D3. The fine regulation of calcium excretion occurs in the distal convoluted tubules and connecting tubules despite the fact that only 10-15% of filtered calcium is reabsorbed there.

Although only 10-15% of filtered Ca2+ is absorbed in the DCT and CNT, these are the main sites in which the fine regulation of Ca2+ excretion and the major action of PTH and activated vitamin D occur. In the DCT and CNT, the luminal voltage is negative and Ca2+ concentration in the lumen is lower than that of plasma. Thus, active transport mechanism against voltage and concentration gradient should exist in these segments. Several Ca2+ transporting proteins are involved in this active transmembrane transport of Ca2+ in the DCT and CNT. Transcellular Ca2+ reabsorption can occur by three steps;

(i) Entry of Ca2+ through the calcium channels (TRPV5, TRPV6) in the apical membrane.

(ii) Binding of Ca2+ with calcium binding protein (calbindin) and diffusion in the cytoplasm (which enables no significant change in the intracellular [iCa2+].

(iii) Ca2+ extrusion via an ATP-dependent plasma membrane Ca2+-ATPase (PMCA1b) and an Na2+/Ca2+ exchanger (NCX1) in the basolateral membrane.

In the collecting duct (CD), there is no evidence that Ca2+ reabsorption occurs even though calcium channel (TRPV6) was documented to be expressed in CD cells. Each renal tubule has a unique environment and plays a different role in Ca2+ reabsorption. The coordinated play of different renal tubules could maintain harmony of renal Ca2+ handling.

**NOTE:**

1. Transient receptor potential (TRP) channel is a superfamily of ion channels permeable to monovalent and/or divalent cations with six-transmembrane domains. The mammalian TRP family consists of six subfamilies and TRPV is Transient receptor potential (vanilloid).
2. The most important effect of vitamin D is to facilitate absorption of calcium from the small intestine. In concert with parathyroid hormone, vitamin D also enhances fluxes of calcium out of bone.

The kidney plays a central role in the regulation of arterial blood pressure. A large body of experimental