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ASSIGNMENT

1. Discuss the role of kidney in glucose homeostasis

Overview of renal glucose homeostasis

The human kidney is involved in the regulation of glucose homeostasis and in abnormalities found in diabetes mellitus via three different mechanisms: (i) release of glucose into the circulation via gluconeogenesis; (ii) uptake of glucose from the circulation to satisfy its energy needs; and (iii) reabsorption into the circulation of glucose from glomerular filtrate to conserve glucose carbon.

Plasma glucose concentrations are determined by the relative rates of glucose entry into, and removal from, the circulation. Normally, despite wide daily fluctuations in the rate of delivery of glucose into the circulation (e.g. meal ingestion) and in the demands of tissues for glucose (e.g. during exercise), plasma levels are maintained within a relatively narrow range throughout the day. Maximal plasma concentrations following meal ingestion are usually < 9.0 mmol/l 2 and minimal concentrations, after moderate fast or exercise, are usually > 3.0 mmol/l 3,4. This is in contrast to other substrates such as glycerol, lactate, free fatty acids (FFAs) and ketone bodies, for which daily fluctuation is much greater 5. Teleologically, this can be explained by the fact that, on the one hand, the body must defend itself from hyperglycaemia, which is associated with both chronic effects (including retinopathy, neuropathy, nephropathy and premature atherosclerosis 6–9) and acute effects (including diabetic ketoacidosis and hyperosmolar hyperglycaemic state, which have significant associated morbidity and mortality); on the other hand, the body must also defend itself against hypoglycaemia, which can cause cardiac arrhythmias, neurological dysfunction, coma, seizures and death 10. Brain function is particularly dependent on having adequate levels of plasma glucose because the brain is unable to either store or produce glucose and alternative sources of energy are either in short supply (e.g. ketone bodies) or are unable to pass the blood–brain barrier (e.g. FFAs) 10.

The precise regulation of plasma glucose concentrations is mainly determined by hormonal and neural factors, which regulate endogenous production of glucose 10. Acute glucoregulatory mechanisms involve insulin, glucagon and catecholamines, which can effect changes in plasma glucose levels over a matter of minutes. Insulin suppresses glucose release in both the liver and kidney by direct enzyme activation/deactivation, as well as by reducing the availability of gluconeogenic substrates and actions on gluconeogenic activators 11. Glucagon has no effect on the kidney, but increases both gluconeogenesis and glycogenolysis in the liver 12. Catecholamines have multiple acute actions, including stimulation of renal glucose release, inhibition of insulin secretion, stimulation of glucagon secretion, and increases in gluconeogenic substrate supply, stimulation of lipolysis and reduced tissue glucose uptake.

Growth hormone, thyroid hormone and cortisol influence glucose levels over a period of hours by altering the sensitivity of the liver, kidney, adipose tissue and muscle to insulin, glucagon and catecholamines, and by altering the activity of key enzymes, which effect glycogen stores and availability of gluconeogenic precursors (lactate, glycogen and amino acids) 10. In the post-absorptive state, glucose uptake by tissues is largely dependent on tissue needs and the mass-action effects of the ambient plasma glucose concentration and, to a lesser extent, on the permissive actions of insulin and counter-regulatory hormones (e.g. thyroid hormones, growth hormone, catecholamines and cortisol). In these circumstances, most uptake of glucose occurs in tissues that do not require insulin (e.g. brain, gastrointestinal tract, renal medulla). However, in the postprandial state, although insulin and other hormones exert greater influence on tissue uptake of glucose, changes in hepatic and renal glucose release into the circulation are still quite important (Table (Table1)1) 10.

## 2. Discuss the process of micturition

### Micturition

Micturition or urination is the process of expelling urine from the bladder. This act is also known as voiding of 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.

### 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.

As mentioned earlier, the process of micturition is governed by both the nervous and muscular systems. Within the nervous system, the process is governed by the autonomous nervous system and the somatic system. Once the urinary bladder reaches its maximum capacity, the stretch receptors in the walls of the bladder send an impulse via the pelvic nerve to the brain via the spinal cord.

The micturition reflex is ultimately generated from the level of the spinal cord after it receives reflexes from the pontine region in the brain. Once the bladder and the urethra receive the signals to empty the bladder, the two sphincters relax and the detrusor muscle causes the contractions of the bladder.

Along with these muscles, the muscles of the abdomen also play a role by putting pressure on the bladder wall. This leads to complete emptying of the bladder.

## 3. Explain the 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 macula densa is a collection of specialized epithelial cells in the distal convoluted tubule that detect sodium concentration of the fluid in the tubule. In response to elevated sodium, the macula densa cells trigger contraction of the afferent arteriole, reducing flow of blood to the glomerulus and the glomerular filtration rate. 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. Lacis cells, also called extraglomerular mesangial cells, are flat and elongated cells located near the macula densa. Their function remains unclear.

## 4. Discuss the role of kidney in 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. Experimental models of spontaneous hypertension, such as the Dahl salt-sensitive rat, have been used to study the effects of kidney transplantation on blood pressure. Results from studies of kidney transplantation indicate that pressure sensitivity to sodium intake 'follows' the kidney, meaning that the recipient of a 'salt-resistant kidney' acquires sodium resistance, and that the recipient of a 'salt-sensitive kidney' acquires pressure sensitivity. The examples above and discussed in this Review demonstrate that it should come as no surprise that most disorders that affect the kidney or the renal vasculature commonly lead to secondary forms of hypertension.

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.

## 5. Discuss the Role of kidney in calcium homeostasis

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. Transient receptor potential vanilloid 5 (TRPV5) and 6 (TRPV6) in the apical membrane act as the main portal of entry, calbindin-D28K delivers Ca2+ in the cytoplasm, and then Na2+/Ca2+ exchanger (NCX1) and plasma membrane Ca2+-ATPase in the basolateral membrane serve as an exit. In the cortical collecting duct, TRPV6 is expressed, but the role might be negligible. In addition to PTH and 1,25(OH)2D3, acid-base disturbance, diuretics, and estrogen affect on these calcium channels. Recently, klotho and fibroblast growth factor 23 (FGF23) are suggested as new players in the calcium metabolism. Klotho is exclusively expressed in the kidney and co-localized with TRPV5, NCX1, and calbindin-D28K. Klotho increases calcium reabsorption through trafficking of TRPV5 to the plasma membrane, and also converts FGF receptor to the specific FGF23 receptor. FGF23:klotho complex bound to FGF receptor inhibits 1α -hydroxylase of vitamin D, and contributes to calcium reabsorption and phosphate excretion in the kidney.