

Renal Physiology

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INTRODUCTION

The kidney is a complex organ with several different functions. One way to remember these functions is to think about a patient who has chronic renal failure. The main features are:

1. Salt and water retention with oedema and hypertension
2. Uraemia
3. Hypercalcaemia and hyperphosphataemia
4. Acidosis and hyperkalaemia
5. Anaemia.

The main functions of the kidney are therefore:

1. Salt and water balance or homeostasis
2. Toxin removal
3. Calcium and phosphate homeostasis
4. Acid–base homeostasis
5. Stimulation of erythropoiesis

Homeostasis means ‘maintenance of the internal environment’ of the body within closely regulated limits. The functions of the kidneys are necessary to maintain this constant environment despite great variation in oral intake and the external environment.

BASIC STRUCTURE OF THE KIDNEYS

The kidney has several layers starting from the outer renal cortex moving deeper to the outer medulla and then to the inner medulla. The specialised structure within the kidney is the nephron. Each kidney contains approximately one million nephrons. Each nephron consists of:

- A glomerulus, which in turn consists of a capillary tuft and a specialised enclosed pouch

like extension of the tubule called the Bowman’s capsule

- The proximal convoluted tubule (PCT)
- The descending thin limb of the loop of Henle
- The ascending thin and thick limb of the loops of Henle
- The vasa recta, which is a series of specialised capillaries which wrap around the loop of Henle
- The distal convoluted tubule (DCT)
- The collecting duct.

The glomeruli sit within the renal cortex and drain into the PCT. This then drains into the descending limb of the loop of Henle, which descends down through the medulla. It then turns back on itself, becoming the ascending limb, and returns to the cortex before becoming the DCT. The DCT drains

Summary

The major functions of the kidneys can be identified by knowledge of the pathological changes seen in renal failure. The kidney has important roles in salt and water, acid-base, electrolyte and calcium homeostasis. These functions are described, including the role of the countercurrent multiplier and exchange systems of the loop of Henle. Where relevant, clinical examples are used to demonstrate the multiple roles of the kidney.

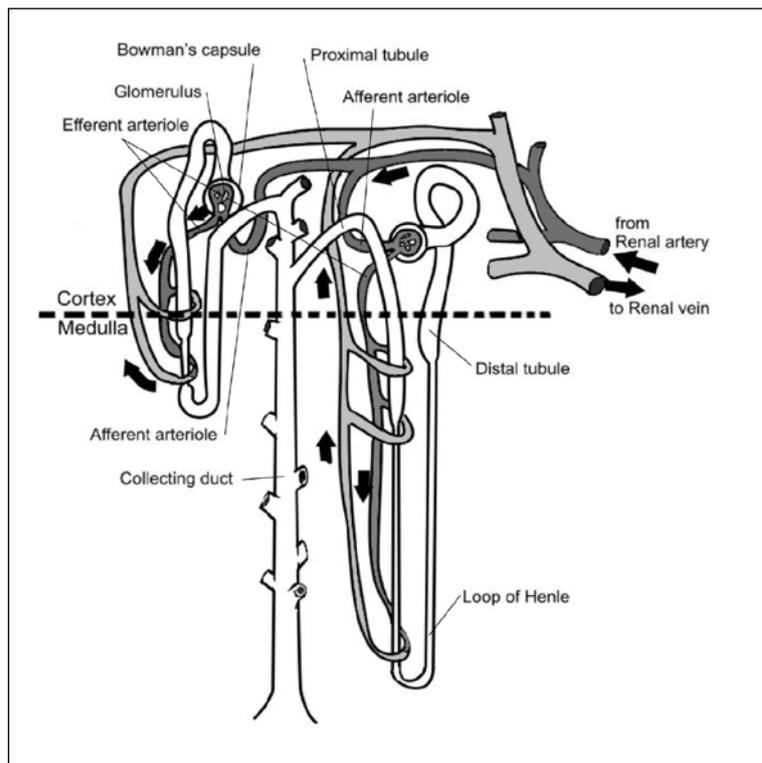


Figure 1. Detailed anatomy of the kidney and nephron

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into a collecting duct which descends back down through the medulla so that urine can drain into the renal pelvis and ureter. Humans have a mixture of short (cortical nephrons) and long (juxta-medullary) nephrons - eighty-five per cent are short in humans. In general the greater the proportion of long loops or length of loop the greater the concentrating ability (for example dogs are able to concentrate urine to greater than 3000mosm.l⁻¹, and some desert animals to greater than 5000 mmosm.l⁻¹)

FUNCTIONS OF THE KIDNEY

Glomeruli

The glomerulus is the filter unit of the nephron. It passively lets water, amino acids, sodium and other free ions pass through its membranes and into the tubule system, but not charged proteins, large proteins or cells. The unique basement membrane, which is at the interface of the capillaries and Bowman's capsule, allows this to happen. Glomerular filtration produces up to 125ml filtrate per minute, most of which needs to be quickly reabsorbed.

Proximal convoluted tubule (PCT)

The PCT is responsible for the majority of the reabsorption. There are four different mechanisms by which solute transport occurs:

1. *Passive diffusion* which occurs across a membrane down an electrochemical gradient, e.g. sodium and chloride ions.
2. *Facilitated diffusion* which is also passive but is more selective as it requires the interaction between an ion and a membrane-bound specific carrier protein, e.g. sodium/amino acid cotransporter.
3. *Passive diffusion through a membrane channel or pore*, e.g. potassium in the collecting duct.
4. *Active transport* against an electrochemical gradient by an energy requiring pump, e.g. the potassium-hydrogen ion antiporter in the collecting duct.

Some transporters within the PCT are responsible for secretion of weak acids and bases. As drugs can be weak acids or bases (e.g.

Table 1. Substances reabsorbed in the PCT

Substance	Approximate % reabsorbed in PCT
Water	65
Sodium	60
Potassium/Chloride/Bicarbonate	80
Glucose	100
Amino acids	100
Calcium	60
Phosphate	80
Urea	50

diuretics) this is one of the renal mechanisms for eliminating drugs from the body. The majority of renal elimination of drugs from the body however is by filtration.

Loop of Henle

The human body has no active pump for water, which can only move across a membrane by osmosis. The role of the Loop of Henle is to create an increasing concentration gradient in the interstitial tissues as the loop passes deeper into the medulla. A gradient from about 285mosm.l⁻¹ in at the beginning of the loop to 1200mosm.l⁻¹ at the apex of the loop is achieved. The collecting ducts pass through this osmotic gradient and so, under the influence of antidiuretic hormone (ADH), water can be retained. The loops of Henle constitute a countercurrent system - the ascending and descending limbs of each loop are parallel, counter to (i.e. opposite in flow) and in close proximity to each other.

There are 3 sections to the loop of Henle:

1. Thin descending limb
2. Thin ascending limb
3. Thick ascending limb

The countercurrent system consists of:

- *A countercurrent multiplier* (the loop of Henle) which sets up an increasing gradient of osmolality as you go to the bottom of the loop.
- *A countercurrent exchange* (the vasa recta) which maintains this gradient. ADH acts to allow uptake of water from the collecting ducts. The osmotic gradient would otherwise gradually diminish as water is reabsorbed by osmosis.

Countercurrent multiplier

Essentially, sodium and chloride (Na⁺ and Cl⁻) leave the ascending limb, which is impermeable to water which therefore cannot follow. Deep in the medulla, Na⁺ and Cl⁻ leave by passive diffusion, however this passive diffusion is not sufficient to maintain such a steep gradient, so in the thick ascending limb sodium is actively pumped out into the interstitium. Water *does* move out of the descending limb into the interstitium by osmosis and this leaves the fluid within the descending limb gradually increasing in osmolality as it moves deeper into the medulla towards the apex of the loop.

It is only as tubular fluid enters the ascending loop that it starts to become less concentrated as Na⁺ and Cl⁻ are actively pumped out (which is where we started). In effect, Na⁺ and Cl⁻ are circulating around the bottom part of the loop which generates the high osmolality in the interstitium.

Countercurrent exchange

The multiplier is self-perpetuating until ADH allows water to be reabsorbed, thereby lowering the osmolality in the interstitium. The vasa recta are also countercurrent in their lay-out and they act in a very similar way to maintain the hypertonicity of the interstitium at the bottom of the loop.

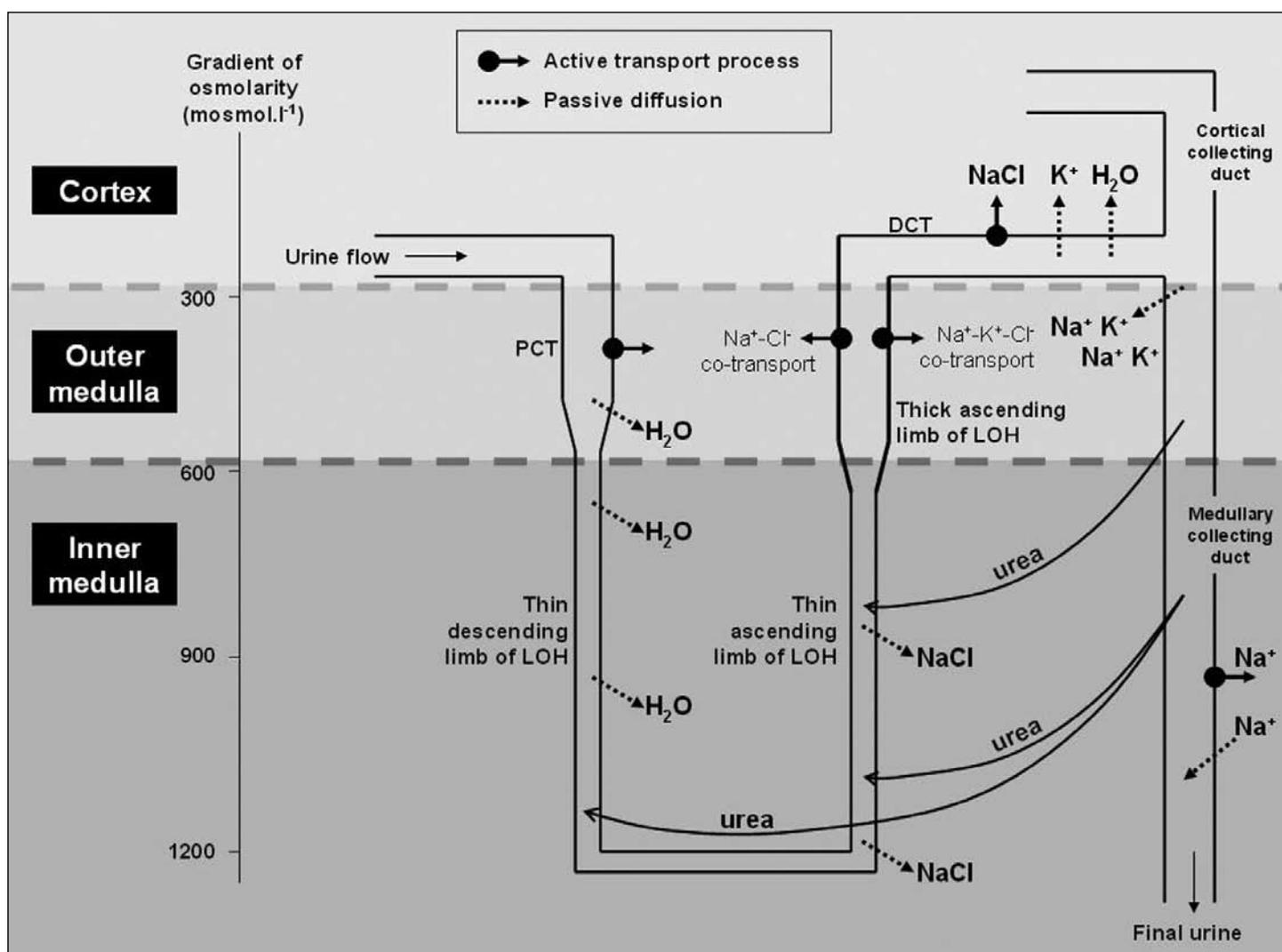


Figure 2. The function of the loop of Henle in concentration of urine

Na⁺ and Cl⁻ diffuse from the ascending vasa into the descending vasa and recirculate around the lowest parts of the loops. At the same time water diffuses from the descending vasa across to the ascending vasa.

The role of urea

The other major factor in generation of the hypertonic medulla is the fact that the collecting ducts are impermeable to urea until the portions deep within the medulla, by which time (after water reabsorption) the urea concentration is very high. When urea reaches this part of the collecting duct, ADH sensitive urea channels allow it to move into the interstitium down a concentration gradient and this further increases the osmolality of the interstitium. Some of the urea diffuses back into the filtrate in the thin limbs of the loop of Henle and some stays within the interstitium.

In summary the important points about the counter current multiplier system are:

1. It is driven by the active reabsorption of the sodium in the thick ascending limb.

2. Different segments of the loop have different permeabilities to water and sodium.
3. Reabsorbed water is rapidly removed from the interstitium into the systemic circulation via the vasa recta.
4. Sodium which is reabsorbed is effectively 'trapped' in the interstitium.
5. The ascending and descending limbs of the same nephron run parallel to each other with the filtrate running in opposite directions.
6. The unique arrangement of the blood supply (the vasa recta) is an essential component in this system.

Distal convoluted tubule (DCT)

The DCT is where the final fine tuning of the reabsorption of many ions such as sodium, calcium, phosphate, potassium, and acid base balance is achieved.

Collecting duct

The collecting duct passes down through the concentration gradient

generated by the countercurrent system. It has varying permeability to water depending on the amount of antidiuretic hormone present and therefore is responsible for concentrating urine. It is also involved with acid secretion (see below)

RENAL BLOOD FLOW

Twenty per cent of the cardiac output (about 1200ml.min⁻¹) goes to the kidney. The amount of blood flow directly affects the rate at which the glomerulus can filter (the glomerular filtration rate - GFR) and subsequently the amount of filtrate produced.

Rate of removal of substance = $\frac{\text{blood flow to organ} \times \text{arteriovenous difference (a-v) in concentration of substance}}$

So to measure renal plasma flow a substance with high extraction is used, for example para-amino hippuric acid (PAH):

Rate of removal in urine (u) = urine concentration x urine volume

Venous concentration is close to zero, so a-v = a

So renal plasma flow (RPF) = $\frac{u \times v}{a} \times \frac{1}{0.9}$

(PAH has an extraction ratio of 90%)

For renal blood flow, multiply by $\frac{1}{1 - \text{haematocrit}}$

Similarly for glomerular filtration rate (GFR), choose a substance which is freely filtered at the glomerulus and neither secreted or re-absorbed, e.g. inulin or creatinine.

GFR = clearance of inulin = $\frac{u \times v}{p}$ where p = plasma concentration

The filtration fraction = $\frac{\text{GFR}}{\text{RPF}} = 0.16-0.2$

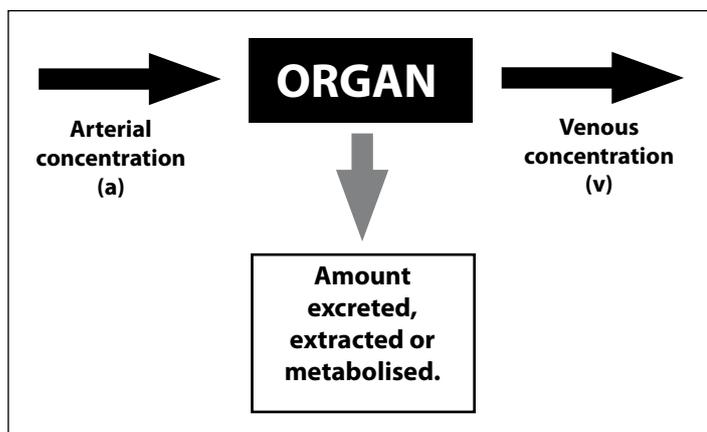


Figure 3. The Fick principle can be used to calculate blood flow for any organ system using a substance that is removed (excreted, extracted or metabolised) by the organ

The blood flow into the glomerulus is via the afferent arteriole and the blood flow out of the glomerulus is by the efferent arteriole.

Altering the radius of either or both of these vessels will alter the pressure within glomerulus. This is called autoregulation, and is achieved with the help of the macula densa, a group of specialised cells which sit within the distal part of the ascending limb of the loop of Henle. They are also in close proximity to the afferent and efferent arterioles. The capillaries and the macula densa together make up the juxtaglomerular complex. If the blood pressure falls there is a decrease in the renal blood flow, and a decreased volume of filtrate. This causes a decreased delivery of sodium and chloride to the macula densa. The macula densa senses this and stimulates the local release of a hormone, renin. Renin converts circulating angiotensinogen to angiotensin I. Angiotensin I is carried to the lungs where it is converted to angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II is then taken back into the systemic circulation and has its effects as outlined in Figure 4.

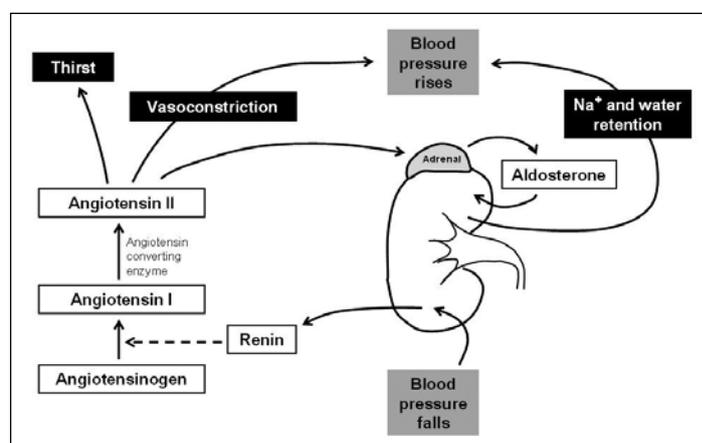


Figure 4. The renin-angiotensin system

Clinical points

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin production and so can impair afferent arteriolar dilatation, reducing GFR. It is for this reason that NSAIDs should be avoided in patients with renal impairment and those who are hypovolaemic and reliant on afferent vasodilatation to maintain GFR.

Patients with *renal artery stenosis* rely on high efferent arteriolar tone to maintain a high filtration pressure across the glomerulus. *ACE inhibitor drugs* are contraindicated in these patients since they inhibit efferent arteriolar constriction (by inhibiting angiotensin II production) and so GFR is dramatically reduced, with consequent deterioration in renal function.

The angiotensin II has four effects:

1. Generalised vasoconstriction causing increased systemic vascular resistance and increasing the blood pressure.
2. Constriction of both the afferent and efferent arteriole but constricting the efferent more. This then increases the differential pressure across the glomerular capillary tuft and increases the GFR.
3. Stimulation of the release of aldosterone from the adrenal gland, which stimulates the reabsorption of sodium from the DCT and collecting duct.

4. Stimulates thirst via an action on the hypothalamus.

Other substances such as nitric oxide and prostaglandins which vasodilate are also released locally in response to altered pressure within the capillary tuft, but the exact mechanisms are poorly understood.

WATER HOMEOSTASIS

Water balance is controlled by antidiuretic hormone (ADH). ADH is released from the posterior pituitary in response to three stimuli:

1. Increased osmolality in the hypothalamus,
2. Decreased plasma volume (cardiopulmonary receptors in the right atrium and pulmonary vessels),
3. Angiotensin II.

Osmoreceptors located in the hypothalamus sense an increase in plasma osmolality and stimulate the release of ADH. Reduced blood pressure is sensed by the atrial stretch receptors and arterial baroreceptors, which also stimulate the release of ADH. ADH release causes an increase in the number of water channels called aquaporins, with in the collecting duct. This facilitates greater water reabsorption by osmosis, as the collecting ducts pass through the concentration gradient generated by the loop of Henle.

SODIUM BALANCE

Approximately 60% of sodium is reabsorbed in the PCT, 20% in the loop of Henle and 5% in the DCT and collecting duct.

There are several mechanisms by which sodium reabsorption or excretion can be affected. The most important are:

1. The renin–angiotensin–aldosterone system
2. Atrial natriuretic peptide

One of the end points of the activation of the renin-angiotensin system is the release of aldosterone. Aldosterone increases sodium reabsorption by increasing the number of sodium channels and the sodium pumps which drive the reabsorption of sodium in the DCT and the collecting duct.

Atrial natriuretic peptide is released in response to atrial stretch, a sign of salt and water overload. This increases the sodium excretion by inhibiting the renin-angiotensin system (see above) and by direct inhibition of the reabsorption of sodium in the collecting duct.

POTASSIUM BALANCE

Potassium is freely filtered by the glomerulus. Almost all of it is then reabsorbed by the PCT. The mechanism at this point is not regulated and does not respond to differing plasma potassium concentrations. The DCT and collecting ducts are responsible for regulating potassium balance by increasing secretion or reabsorption.

There are two clinically important mechanisms for potassium exchange. Aldosterone stimulates potassium secretion by increasing sodium reabsorption. Sodium is reabsorbed in exchange for potassium by an active transporter. Thus drugs such as spironolactone which antagonise aldosterone can cause hyperkalaemia.

Box 1. ADH and the renin-angiotensin systems are demonstrated by the body's response to different haemodynamic challenges:

1000ml 0.9% saline intravenously - a response to a small increase in volume

This is a volume load but it is isotonic. The volume expansion is initially 1000ml which distributes quickly into the extracellular fluid - about 250ml stays in the intravascular volume, the remainder fills the interstitial space:

- ↑ blood volume stimulates cardiopulmonary stretch receptors (right atrium)
- posterior pituitary → ↓ADH secretion
- ↓ thirst and diuresis

1000ml blood intravenously - a response to a large increase in volume

This volume stays in the intravascular compartment.

Acute response

- stimulates the baroreceptors of the arterial system (carotid & aortic sinuses)
- via the glossopharyngeal and vagus nerves
- reflex ↓ cardiac output and ↓ vascular tone

Slower response

- ↓ activation of renin-angiotensin system
- ↓ aldosterone secretion

1000ml 5% glucose intravenously or water orally - a response to a decrease in osmolality

This constitutes less of a volume load since it is distributed into the entire body water. One twelfth stays in the intravascular space (83ml). Oral water is similar since it is rapidly absorbed from the stomach. However it does cause plasma dilution and ↓ osmolality:

- detected by osmoreceptors of the hypothalamus
- ↓ ADH secretion

The response to hypokalaemia in the collecting duct is to stimulate the uptake of potassium from the filtrate by activating the potassium ion-hydrogen ion exchange pump. This secretes hydrogen ions into the collecting duct in exchange for reabsorbing potassium ions. This is why hypokalaemic patients are often alkalotic. This pump is also stimulated by acidosis and is one of the reasons why acidotic patients are often hyperkalaemic.

The kidney can maintain normal serum potassium concentration down to low GFRs. When the kidneys potassium handling ability finally fails the patient becomes hyperkalaemic due to the low quantities of blood being filtered and the inability of the kidney to respond by secreting increased levels of potassium. Faecal excretion of potassium is up-regulated to help maintain serum potassium as the kidney fails.

TOXIN REMOVAL

Toxins are removed by two mechanisms:

1. Filtration
2. Secretion

Most water soluble toxins such as creatinine are freely filtered and not reabsorbed. Therefore the levels should remain constant and at non-toxic levels in the blood unless ingestion, production or GFR changes.

Some toxins are removed from the blood by active secretion in the PCT. Drugs such as diuretics and trimethoprim are removed in this way.

CALCIUM AND PHOSPHATE HOMEOSTASIS

The kidney plays a major role in calcium homeostasis, along with the skeleton and intestine. The intestine allows calcium and phosphate to be absorbed from the diet. The skeleton is the store of calcium. The kidney has two roles:

1. The activation of vitamin D (via addition of a second hydroxyl group) which then facilitates calcium absorption from the digestive tract.
2. The tubular reabsorption and excretion of calcium and phosphate respectively under the influence of parathyroid hormone.

Vitamin D stimulates the absorption of both calcium and phosphate from the intestine and is part of the feedback mechanism which controls plasma levels of these ions.

ACID BASE BALANCE

Maintenance of a constant pH is very important for the body as many of our enzyme systems are very pH sensitive. Both acids and alkalis are generated from the diet either by direct ingestion or by generating an acid or an alkali after metabolism. There is usually a net acid production.

Bicarbonate is the main buffer in the human body. As almost 100% of bicarbonate is filtered by the kidney, to help maintain the pH in the body the bicarbonate must be reabsorbed. This is mainly done by the PCT which acidifies the urine. The pH falls from 7.3 to 6.7 along the length of the PCT.

The PCT reabsorbs bicarbonate by secreting hydrogen ions into the lumen of the tubule. The enzyme carbonic anhydrase catalyses the conversion of the hydrogen ion and the bicarbonate ion into water and carbon dioxide within the tubule. The carbon dioxide then diffuses back into the cell where carbonic anhydrase catalyses the

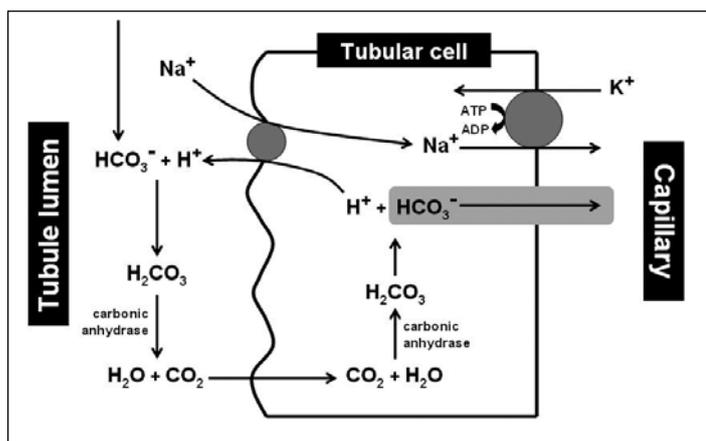


Figure 5. Bicarbonate reabsorption in the PCT

reverse - carbon dioxide combines with water to form bicarbonate, which is reabsorbed into the blood stream, and a hydrogen ion, which is recycled to be used to reabsorb another bicarbonate ion. The mechanism of bicarbonate reabsorption does not cause a net loss of hydrogen ions and does not excrete any of the acid produced by the body.

The distal nephron then reclaims any of the bicarbonate that remains in the filtrate after passing through the PCT.

Although when the filtrate reaches the collecting duct it is acidic, this is because of the reabsorption of bicarbonate not the excretion of acid. As stated previously there is an excess of acid generated by metabolism that the body needs to excrete. Although the vast majority is achieved by carbon dioxide excretion by the lungs, an important fraction (particularly phosphate and sulphate ions) is excreted by the collecting duct. Hydrogen ions are actively secreted by the hydrogen ion-potassium ion antiporter (see above). This would result in a sharp increase in the acidity of the urine if the hydrogen ions were not buffered. As all the bicarbonate has been reabsorbed, the hydrogen ions are buffered primarily by ammonia, created from glutamine in the renal tubular cells and filtered phosphate ions.

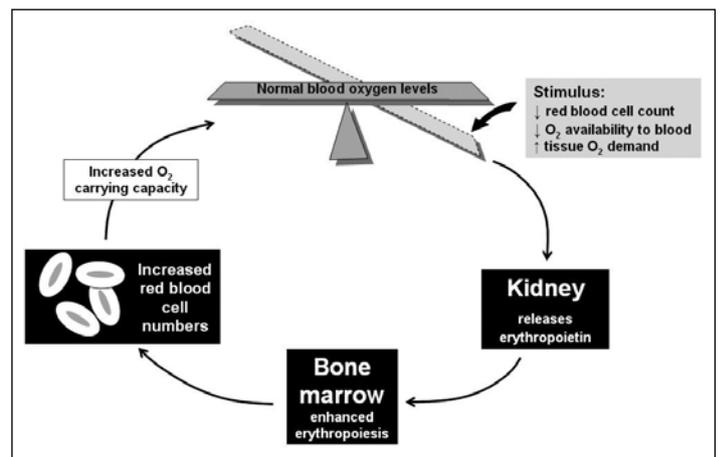


Figure 6. Regulation of erythropoiesis by erythropoietin

ERYTHROPOIESIS

The kidney responds to hypoxia and decreased red blood cell mass (decreased oxygen carrying capacity) by releasing erythropoietin which stimulates the bone marrow to produce more red blood cells (Figure 6).

CONCLUSION

This article provides an overview of the major functions of the kidney. A clear understanding of these concepts is essential for safe administration of drugs during anaesthesia, particularly in those with impaired renal function. A logical knowledge of the physiology of the renal system allows recognition and appropriate management of patients with renal failure, particularly in patients with critical illness.