Introduction

Little has changed in our basic physiological understanding of the kidneys in the last 70 years. Indeed, the renal system functions to maintain acid-base homeostasis, eliminate detoxified substances, and regulate the plasma ion concentration and volume in response to endogenous or exogenous stimuli.\textsuperscript{1–3} The by-product of these processes is the production of urine, the composition of which changes according to the physiological needs of the individual. Additionally, the kidneys also produce hormones such as renin, erythropoietin, and the active form of vitamin D.\textsuperscript{4}

This article serves as a summary of some important concepts that occur relating to renal function: tubuloglomerular feedback, ion exchange in the nephron, and the countercurrent multiplier and exchange systems.

Relevant anatomy (Figure 1)

There are normally two functioning kidneys in the human body located within the confines of the retroperitoneum. Each kidney is made up of about a million specialised, functional units called the nephron. There are two broad groups of nephrons, aptly named for their location either in the cortex or close to the medulla of the kidney. Each nephron has different tubular sections starting with the Bowman’s capsule, which houses a tuft of capillaries known as the glomerulus, with its own afferent and efferent arterioles. Together, the Bowman’s capsule and glomerulus are referred to as the renal corpuscle. The Bowman’s capsule then connects to the proximal convoluted tubule, followed by descending then ascending thick and thin loops of Henle. Finally, the distal convoluted tubule connects the loop of Henle to the collecting duct, which coalesces with other collecting ducts to form the renal pelvis. The renal pelvises drain into the ureter allowing the plasma ultrafiltrate to be escorted to the bladder for safekeeping until excretion. Collecting ducts or tubules have two segments, again named for their location within the kidney – cortical and medullary collecting ducts.\textsuperscript{1,2,4}

The juxtaglomerular apparatus (JGA) is a special intersection in the nephron of the kidney where the distal convoluted tubule takes a turn to lie next to the Bowman’s capsule. This area of the distal convoluted tubule contains specialised tubular cells called the macula densa, which are sensitive to changes in sodium and chloride concentrations in the tubular fluid. The apparatus not only houses the macula densa but also contains special smooth muscle arteriolar cells called granular cells, which contain secretory granules.\textsuperscript{1,2,4}

Autoregulation

The kidneys do not function independently. There are complex communication channels that regulate the glomerular filtration rate (GFR), ultimately altering renal tubular secretion and reabsorption to maintain homeostasis, somewhat akin to traffic lights at a busy intersection. The GFR refers to the rate at which blood is filtered by the glomerulus in the renal corpuscle. There are two broad mechanisms responsible for maintaining a steady
GFR, the myogenic mechanism and the tubuloglomerular feedback mechanism.1

**Myogenic mechanism**

Smooth muscle cells in the walls of the afferent arterioles of the glomerulus respond to changes in blood pressure. If the blood pressure increases, the arterioles constrict to prevent excessive filtration and with a reduction in blood pressure the arterioles will dilate to maintain an adequate GFR.1 Specialised cells located between the glomerular capillaries, called mesangial cells, aid in this mechanism by contracting or relaxing in response to signals from the macula densa. Contraction reduces the surface area available for filtration, while relaxation increases it, influencing the GFR.1

**Tubuloglomerular feedback mechanism**

If the GFR rises due to increased blood pressure, there will be a correlating increase in tubular fluid flowing past the macula densa (because more fluid is filtered). As the amount of tubular fluid increases, the amount of sodium filtered also increases. This is sensed by the macula densa and results in the release of adenosine triphosphate (ATP) and adenosine, which act on the afferent arteriole of the glomerulus and cause it to constrict. This afferent arteriolar constriction serves to normalise the GFR once more. If there is a decline in the GFR, the opposite will occur. In a power play, the macula densa also secrete nitric oxide that can stop the action of ATP and adenosine, which would otherwise cause the afferent arteriole of the glomerulus to constrict.1

**Hormonal influences on the GFR**

**Renin-angiotensin-aldosterone system (RAAS)**

This multisystemic feedback mechanism helps regulate the body’s fluid balance and blood pressure. Specialised cells in the JGA release renin in response to a decrease in blood pressure or sodium levels. Renin initiates a cascade of events ultimately leading to the cleavage of angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin II by a converting enzyme and this hormone causes the “angios” to “tense”. This intense vasoconstriction is paired with the release of aldosterone from the adrenal glands, which then acts on the distal convoluted tubule and collecting ducts to increase sodium (and thus also water) reabsorption. The result is an elevation of blood pressure due to an increase in circulating blood volume and an increase in systemic vascular resistance via vasoconstriction.1

**Antidiuretic hormone (ADH)**

Also known as vasopressin, ADH acts in the collecting ducts to prevent diuresis. It is released from the posterior pituitary gland in response to changes in blood osmolality. In response to ADH release, aquaporins emerge in the cells of the collecting ducts rendering them more permeable to water reabsorption (thus reducing water excretion). The result is water reabsorption and the excretion of concentrated urine.1

**Atrial natriuretic peptide**

This hormone is secreted by the atria in the heart in response to high blood pressure. When released, the hormone promotes sodium and water excretion by inhibiting the release of aldosterone. Without aldosterone present, sodium (and water) reabsorption in the distal tubules is reduced.1

The various renal tubular feedback mechanisms are tightly interconnected and coordinated to ensure overall homeostasis. Changes in blood pressure and fluid balance can alter hormone secretion, directly affecting renal arteriolar tone and thus the GFR. Simultaneously, electrolyte reabsorption or secretion is enhanced to maintain the plasma-ion concentration following the body’s needs. Other influences on the GFR, such as calcium homeostasis, sympathetic control, and the role of the baroreceptor reflex, as well as the influence the filtration coefficient can have on the GFR, are not discussed in this summary. Let us now delve deeper into the streets of each segment of the nephron.

**Ion exchange mechanisms**

Akin to the busy streets of a city, each segment of the nephron is like an intersection with different capabilities in terms of which ions are reabsorbed or secreted into tubular fluid. Additionally, different transport mechanisms facilitate the transport of ions across the cells of different segments of the nephron. Water reabsorption in the nephron generally follows sodium reabsorption, but certain segments of the nephron are impermeable to water unless facilitated by hormonal feedback. We can consider these gated communities where an entrance fee is required.

**Transport mechanisms**

There are several transport mechanisms used in the nephron to transport ions across cell membranes, either into tubular fluid or back across into the intravascular space (see Figure 2).

**Passive diffusion**

Ions follow a concentration gradient and move from high to low concentrations.6 This is similar to the flow of traffic from the central business district (CBD) of a city to the quieter suburbs.

**Active transport**

Ions move against their concentration gradient and require help in the form of ATP to achieve this. Of importance is the sodium-potassium adenosine triphosphatase pump (Na/KATPase), which actively transports sodium out of cells and potassium into cells against their concentration gradients.2 This can be considered analogous to having to go back to work in the CBD and realising there will be no parking, so you hop in a metered taxi.

**Secondary active transport (co-transport)**

This is the movement of two ions, one down its concentration gradient and one against. The ion moving along its concentration gradient releases the energy required to move the other ion.
against its concentration gradient. Similar to passengers in a bus, some are going home to quiet suburbs while others are headed in busier directions.

**Counter-transport**

This transport mechanism moves two ions in opposite directions across a cell membrane. Think of pedestrians crossing the street in opposite directions.

**Facilitated diffusion**

Ions move across a membrane with the help of carrier proteins. These proteins assist in the transport of specific ions or molecules across a membrane, usually down their concentration gradient. Parents of children will understand that these little ones are best transported from busy areas to quieter areas in a pram.

**Paracellular transport**

This refers to the movement of ions between cells through the tight junctions that connect cells. This pathway allows for the passive movement of ions based on concentration gradients. This mechanism is particularly important for the movement of water and small ions. Think of the minibus taxi that sneaks past you standing still at a red traffic light.

**Ion exchange in the nephron: sodium handling (Figure 3)**

**Proximal convoluted tubule**

Of the sodium load presented to the proximal convoluted tubule, 65–70% is reabsorbed. Sodium gains entrance into the tubular cell across the luminal membrane via two mechanisms. The first is co-transport with nutrients and the second is counter-transport with hydrogen ions, or ammonium. Both of these transport mechanisms involve the movement of ions against their concentration gradient. Similar to passengers in a bus, some are going home to quiet suburbs while others are headed in busier directions.

**Figure 2: Transport mechanisms common in the nephron**

**Figure 3: Sodium handling by the nephron**
mechanisms depend on the Na/K ATPase, which reduces the concentration of sodium in the cell and maintains a negative intracellular potential. Three sodium ions are reabsorbed for every two potassium ions secreted using this ATPase. There is a constant amount of sodium and water reabsorption that occurs independent of the GFR due to oncotic pressure in the peritubular capillaries, otherwise, sodium reabsorption generally matches the GFR in this part of the tubule.2,4,6

**Thick ascending limb of the loop of Henle**

In this part of the tubule, once again a Na/K ATPase is creating a negative intracellular gradient allowing sodium to be transported from the tubular lumen across the luminal membrane via two mechanisms. The first is co-transport with potassium and chloride (Na/K/2Cl). The second is counter-transport with hydrogen ions.2,4

**Distal convoluted tubule**

Again, the Na/K ATPase pump is hard at work creating a negative intracellular environment. In this part of the tubule, sodium is reabsorbed from tubular fluid via special sodium-channels and also by co-transport with chloride.2,4

**Collecting ducts**

Sodium reabsorption in this part of the nephron involves the principal cells of the collecting ducts, which contain sodium-channels. Sodium moves down its concentration gradient once again due to the action of the Na/K ATPase located on the basal aspect of the cell.2,4

**Ion exchange in the nephron: water reabsorption**

The descending thin limb and the bend towards the ascending thick limb of the loop of Henle are freely permeable to water. Thereafter the thick ascending limb and the distal convoluted tubule are impermeable to water movement. The collecting duct is partially permeable to water through the action of ADH, which inserts aquaporins to enhance water reabsorption. Generally speaking, water will be reabsorbed with sodium creating an osmotic gradient between the tubular fluid and capillaries.2

**Ion exchange in the nephron: chloride handling**

Chloride exchange in the nephron can occur via transcellular and paracellular mechanisms.

**Thick ascending limb of the loop of Henle**

We recall that chloride is reabsorbed in this part of the tubule along with sodium and potassium in a co-transporter system.2

**Distal convoluted tubule**

Chloride again moves with sodium from the tubular fluid into the cell with a co-transporter.2

**Collecting ducts**

Type B intercalated cells facilitate chloride movement here using a counter-transport mechanism with bicarbonate, which is dependent on the basal hydrogen ATPase. Chloride is then reabsorbed through chloride-specific channels.2

**Ion exchange in the nephron: glucose handling**

All of the glucose contained in the tubular fluid is reabsorbed in this part of the tubule. This is through co-transport with sodium, as previously discussed. If there is too much glucose in the tubular fluid the reabsorption capability of the tubule at this point is overwhelmed and glucose will begin to appear in the urine. This phenomenon is termed the transport maximum. At a normal GFR of 125 ml/min, glucose will appear in the urine at a threshold of about 10–12 mmol/l. Glucose transport mechanisms in this part of the tubule will be fully saturated at around 15 mmol/l, again if the GFR is normal.2

**Ion exchange in the nephron: urea and protein reabsorption**

Proximal convoluted tubule

This part of the tubule reabsorbs 50% of the urea load in the tubular fluid through passive diffusion.2
Medullary collecting ducts

Another 10% of the urea load is reabsorbed here. The permeability of this part of the nephron to urea is improved through the action of ADH.2

Proteins

The glomerular membrane is mostly impermeable to proteins, which are generally too large to cross the membrane. Some albumin does pass through the glomerulus and most of this load will be reabsorbed by the tubules. Large proteins are transported via endocytosis. There also exists a transport maximum for proteins and normal urine protein content averages about 100 mg per day.2

Ion exchange in the nephron: potassium handling

Thick ascending limb of the loop of Henle

Potassium is reabsorbed along with sodium in this part of the nephron with the help of a co-transporter along with chloride (Na/K/2Cl).2

Distal convoluted tubule and cortical collecting duct

Special type A cells reabsorb potassium into the blood in this part of the nephron whilst principal cells secrete potassium into the tubular fluid. The cortical collecting duct is an important area for potassium exchange compared with other parts of the nephron.2

Medullary collecting duct

This part of the tubule reabsorbs potassium but never secretes it. The net effect of these processes is that there is usually potassium that will appear in the urine, depending on intake. During states of potassium depletion, reabsorption will predominate.2

Ion exchange in the nephron: hydrogen secretion and bicarbonate reabsorption (Figure 5)

These processes occur in most parts of the nephron.

Proximal convoluted tubule

Using a counter-transport mechanism, hydrogen is secreted in exchange for sodium reabsorption. Bicarbonate is also reabsorbed in this part of the tubule with hydrogen secretion using a hydrogen transporter on the luminal edge of the cell. This reacts with filtered bicarbonate in the tubular fluid to generate carbonic acid, which then dissociates into carbon dioxide and water. The carbon dioxide diffuses back into the cell and combines with water in the cell to again form carbonic acid. Inside the cell, this reaction generates more hydrogen ions that are secreted and bicarbonate ions that are reabsorbed.2

Thick ascending limb of the loop of Henle

Hydrogen is secreted here into the tubular fluid in exchange for sodium ions, which are absorbed into the cell with a hydrogen-sodium (H/Na) counter-transporter.2

Distal convoluted tubule

Here hydrogen secretion into the tubular fluid uses a hydrogen transporter. In the tubular fluid, hydrogen reacts with hydrogen phosphate ions to produce phosphoric acid, which is excreted. Bicarbonate is generated in the cell via the reaction of carbon dioxide with water using carbonic anhydrase and is then reabsorbed.2

Medullary collecting ducts

A hydrogen-potassium (H/K) exchanger facilitates potassium reabsorption and hydrogen ion excretion.2,4

Countercurrents

Countercurrent multiplier

The countercurrent multiplier exists to create a tonic renal interstitium that increases in tonicity with increasing depth into the renal medulla. This mechanism occurs in the loop of Henle. It is made possible because the descending limb of the loop of Henle is impermeable to solute and permeable to water.
The ascending limb is impermeable to water and permeable to solute using the Na/K/2Cl co-transporter to pump out solute.1,2,4,6

**Countercurrent exchanger: the vasa recta**

Vasa recta is the name given to the capillaries in the renal medulla, which are also shaped in hairpin bends that are tucked into the loop of Henle. Flow in the vasa recta is in the opposite direction to the flow of fluid in the tubule. This allows the tonic gradient, which is generated by the loop of Henle with the countercurrent multiplier, to be maintained. If the vasa recta were linear, electrolytes would move in and out of the capillary and the tonicity of the interstitium would be lost.1,2,4,6

**Conclusion**

The renal function relies on a complex network of feedback mechanisms from the body regulating the GFR and allowing water and ions to be reabsorbed and excreted as needed to achieve homeostasis. Akin to the streets of a busy city, the movement of ions across cells in the nephron is complex and tightly regulated. A thorough understanding of these networks and ion movements is vital for all anaesthetists.

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**References**