Chapter

Potassium Homeostasis

Shakuntala S. Patil and Sachin M. Patil

Abstract

The average potassium intake in the United States population ranges from 90 to 120 mEq/day. About 98% of the total body's potassium is intracellular, and only 2% is present in the extracellular compartment. This distributional proportion is essential for cellular metabolic reactions and maintaining a gradient for resting membrane potential. A loss of this gradient results in hyper- or hypopolarization of the cell membrane, especially in cardiac muscles leading to life-threatening arrhythmias. Multiple mechanisms in human maintain homeostasis. Transient initial changes are due to transcellular shifts activating sodium-potassium ATPase pumps on the cell membrane. The kidneys essentially take part in excess potassium excretion, maintaining total body stores constant within normal range. Gastrointestinal secretion of potassium is insignificant in individuals with normal renal function, however plays an essential role in individuals with compromised renal function. So far, a classic feedback mechanism was thought to maintain potassium homeostasis; however, a recently recognized feedforward mechanism acting independently also helps preserve potassium homeostasis. Hence, potassium homeostasis is vital for humans to function at a normal level.

Keywords: potassium, homeostasis, gradient, renal, compartment

1. Introduction

The total body potassium (K^+) in an average 70-kg adult is approximately 3000–4000 mEq (50–55 mEq/kg) [1]. About 98% of this is intracellular, approximating to a concentration of 140 mEq/L and 2% in the extracellular compartment, which amounts to 4–5 mEq/L. Potassium's two primary physiologic functions are cellular metabolism, protein, glycogen, deoxyribonucleic acid (DNA) synthesis, and resting potential membrane maintenance. Multiple physiologic processes have been identified in humans that maintain potassium homeostasis with a goal of appropriate tissue potassium distribution [1]. They can be classified into two groups based on the mechanisms involved: transcellular shifts and potassium excess excretion.

Transcellular mechanisms maintain the ICF (intracellular fluid): ECF (extracellular fluid) potassium ratio by acting immediately within the first few minutes to hours by regulating Na^+/K^+-ATPase (sodium/potassium adenosine triphosphatase pump), resulting in transcellular shifts. It is an electrogenic pump transporting sodium and potassium in the ratio of three sodium to two potassium. It is an integral membrane protein and serves as an ion channel, maintaining the electrochemical gradient

across the cell membrane. The delayed mechanisms are slower to kick in but play a significant role in the excretion of the excess potassium from the body *via* renal and gastrointestinal mechanisms.

2. Potassium homeostasis mechanisms

2.1 Factors responsible for the transcellular shift of potassium

2.1.1 Insulin

Insulin is released after a meal when the plasma glucose concentration increases. Insulin plays a vital role in shifting dietary potassium into the cells and avoiding hyperkalemia before the kidneys can work on the excretion of the extra potassium [2, 3]. Insulin attaches to specific cell surface receptors and inserts GLUT4 (glucose transporter type-4) into the cell membranes, promoting glucose uptake in insulin-responsive tissues such as skeletal muscles, adipocytes, and cardiomyocytes. More than 80% of glucose is transported into the muscle cells. Also seen is an upregulation of the GLUT4-mediated glucose transport in elevated transport needs, like elevated blood glucose during a carbohydrate-rich meal or during increased metabolic demands by skeletal muscles during exercise [4]. The potassium uptake is also increased during this process by increasing the Na^+/K^+-ATPase activity. Insulin is also noted to have differential glucose and K uptake regulation, as noted in a metabolic syndrome where insulin-mediated glucose is compromised, but the cellular K+ uptake usually occurs [5, 6].

2.1.2 Catecholamines

Catecholamines play a critical role in potassium homeostasis. They alter internal K^+ distribution by acting through alpha and beta receptors. Beta-2 receptors enhance K^+ uptake by cells by activating the Na^+/K^+-ATPase pump [7, 8]. This effect appears to be present at basal catecholamine levels [9, 10]. The beta-adrenergic activity also increases insulin secretion from the pancreas by directly stimulating and enhancing glycolysis, which increases blood glucose levels. A stress response results in epinephrine release that causes an acute drop in plasma K^+ by approximately 0.5– 0.6 mEq/L. Alpha-1,2 adrenoreceptors mediate the initial hyperkalemia by activating hepatic calcium-dependent potassium channels [11, 12]. Beta-3 adrenoreceptor stimulation may also affect the plasma potassium [12].

2.1.3 Exercise

Exercise causes an elevation in plasma K^+ levels. The rise is proportional to the exercise intensity. There is an increase of 0.3–0.4 mEq/L with slow walking, 0.7–1.2 mEq/L with moderate exercise, and a max of 2.0 mEq/L with strenuous exercise leading to exhaustion [13–15]. These changes are transient for few minutes and then normalize. This transient increase is due to the release of potassium from the exercising cells. Skeletal muscle cells have ATP-dependent K^+ channels. A reduction of ATP (adenosine triphosphate) levels causes the opening of more K^+ channels. The release of potassium from the muscles causes a local increase in the plasma K^+ concentration, which causes vasodilation, and hence increases blood supply to the muscles during

exercise. This mechanism is attenuated in physical conditioning as there is an increase in both cellular K^+ concentration and Na^+/K^+-ATPase activity.

2.1.4 Acid-base balance changes

The changes in acid-base balance cause alterations in K^+ levels to maintain electroneutrality. Hence, such changes are seen only in the setting of acidosis caused by inorganic acids. Electroneutrality is maintained by the movement of K^+ and Na^+ into the ECF, as chloride (Cl^-) movement into the cells is limited. The wide range of variation is possibly due to other mechanisms involved in regulating potassium homeostasis [16, 17].

Skeletal muscles also have another mechanism to regulate intracellular pH *via* Na^+-H^+ exchanger present on the cell membrane to regulate intracellular pH. The exact mechanism is explained in **Figure 1**.

2.1.5 Plasma tonicity

The changes in plasma tonicity also affect K^+ levels. Effective osmoles such as glucose, mannitol, and sucrose accumulate in the ECF, resulting in an osmotic gradient that causes water movement from ICF to ECF [18–20]. This effect leads to a decrease in cell volume. During this process, the intracellular K^+ concentration increases and causes K^+ efflux through K^+ permeable channels. This process is shown in **Figure 2**.

2.1.6 Plasma K^+ concentration

The plasma K^+ concentration itself influences the movement of K^+ in and out of cells *via* passive mechanisms, hence regulating the homeostasis. For example, there is

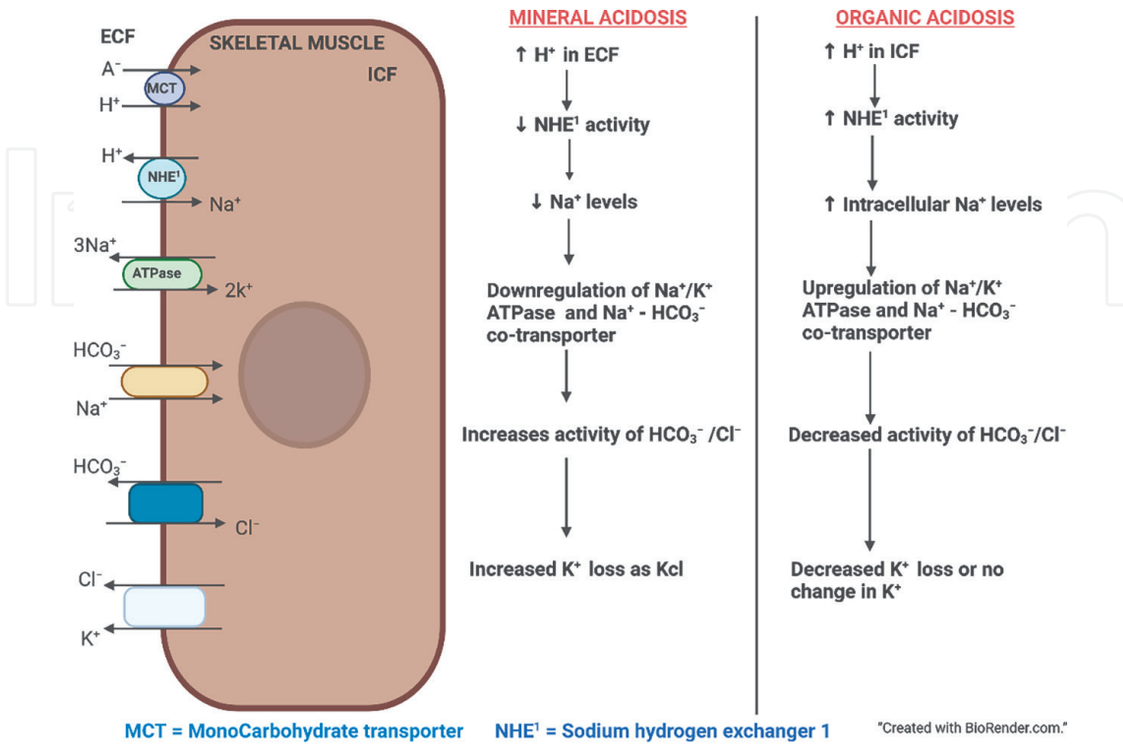

Figure 1.
Intracellular pH regulation by skeletal muscles.

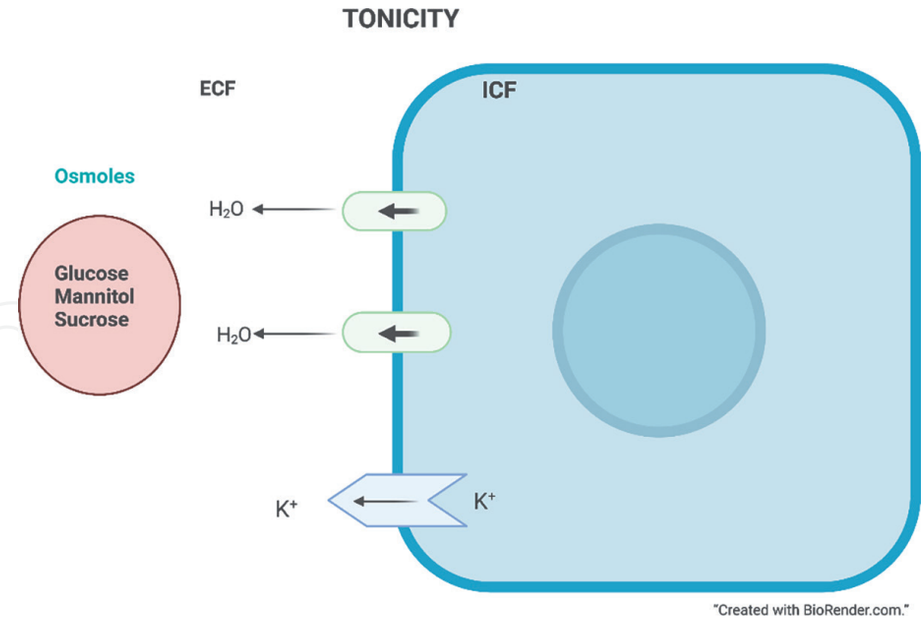

Figure 2.
Plasma tonicity.

an initial elevation of plasma K^+ concentration after a K load, promoting K^+ movement inside the cells. Similarly, in K^+ losses either *via* gastrointestinal or renal processes, there is an initial fall in plasma K^+ level in the plasma within the required normal range transiently, unless the total body K^+ stores are significantly affected [21, 22].

2.1.7 Effect of cell breakdown and production on plasma potassium

Clinical conditions such as severe trauma, tumor lysis syndrome, acute tissue ischemia, and necrosis cause cell breakdown and release of intracellular K^+ into the ECF [23]. The hyperkalemia severity is dependent on the ability of other cells to uptake the excess K^+ and the capability of the kidney to excrete K^+ quickly. Conversely, there is a movement of ECF K^+ to ICF due to increased cellular metabolic needs like protein synthesis in situations with increase in rapid cell production. This effect is observed in cases of severe vitamin B 12 or folic acid deficiency. When such individuals are supplemented with vitamin B 12 or folic acid, there is a marked increase in erythropoiesis and red blood cell production, causing hypokalemia; hence, it is recommended to monitor labs and supplement potassium to replete the levels [24].

2.2 Factors responsible for potassium excretion (renal)

The kidney plays a significant role in the excretion of excess K^+ and maintaining K^+ balance. The colon plays a trivial role as small amounts of K^+ are lost through feces each day. Insignificant amounts are lost through sweat.

2.2.1 Potassium handling in proximal convoluted tubule (PCT)

Around 80% of the filtered potassium is reabsorbed in the proximal collecting tubule. The movement of K^+ in the PCT is mainly passive, following sodium and water. The Na^+ absorption increases across the PCT, by both active and passive processes causing net fluid reabsorption. This process drives K^+ reabsorption by solvent

drag. There is also a minimal change in the transepithelial voltage from negative to slightly positive as we move down the PCT, favoring K^+ and calcium (Ca^{2+}) reabsorption *via* the paracellular pathway (**Figure 3**) [2].

2.2.2 Potassium handling in thick ascending limb

K^+ reabsorption in this segment occurs by both paracellular and transcellular pathways. $Na^+/K^+/Cl^-$ co-transporter plays a significant role in the reabsorption of potassium here. This channel is located on the luminal side. The low-intracellular Na^+ concentration and high-transcellular Na^+ gradient caused by the Na^+/K^+-ATPase pump activity in the basolateral membrane help activate the $Na^+/K^+/Cl^-$ co-transporter. This electroneutral process causes an increase in intracellular K^+, which then exits *via* the K^+/Cl^- co-transporter located in the basolateral membrane. A ROMK (renal outer medullary potassium channel) is present on the luminal side, allowing K^+ out of the cell into the lumen. This activity helps maintain the $Na^+/K^+/Cl^-$ co-transporter activity by recycling the K^+ (**Figure 4**) [2, 25].

2.2.3 Potassium handling in distal convoluted tubule (DCT) and collecting duct

Less than 10% of the filtered load reaches the distal tubule. The lumen's K^+ concentration increases down the lumen and is secondary to voltage-dependent K^+ secretion mediated by the ROMK channel. Late DCT has an epithelial Na^+ channel (ENaC) responsible for sodium absorption and creating lumen-negative electrochemical gradient and hence effusion of K^+, similar to collecting duct [26].

Most potassium secretion is in the connecting segment and the collecting tubules (cortical, outer medullary, and inner medullary). This secretion varies according to the physiologic needs of the body. The connecting tubule has two major types of cells: principal cells and intercalated cells.

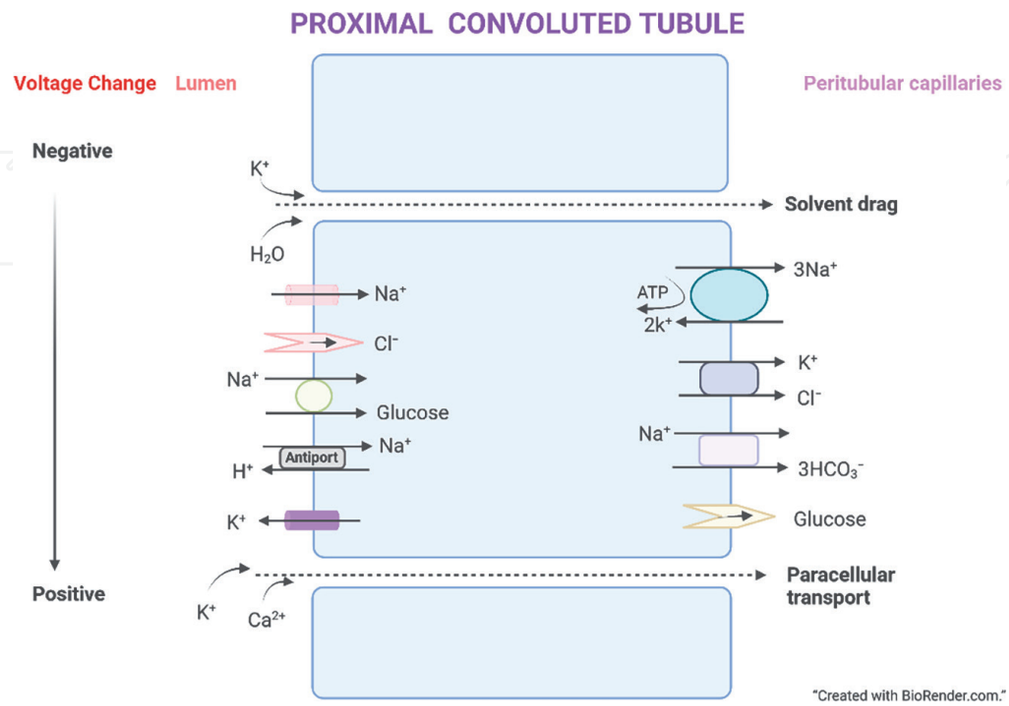

Figure 3.
Potassium handling in proximal convoluted tubule (PCT).

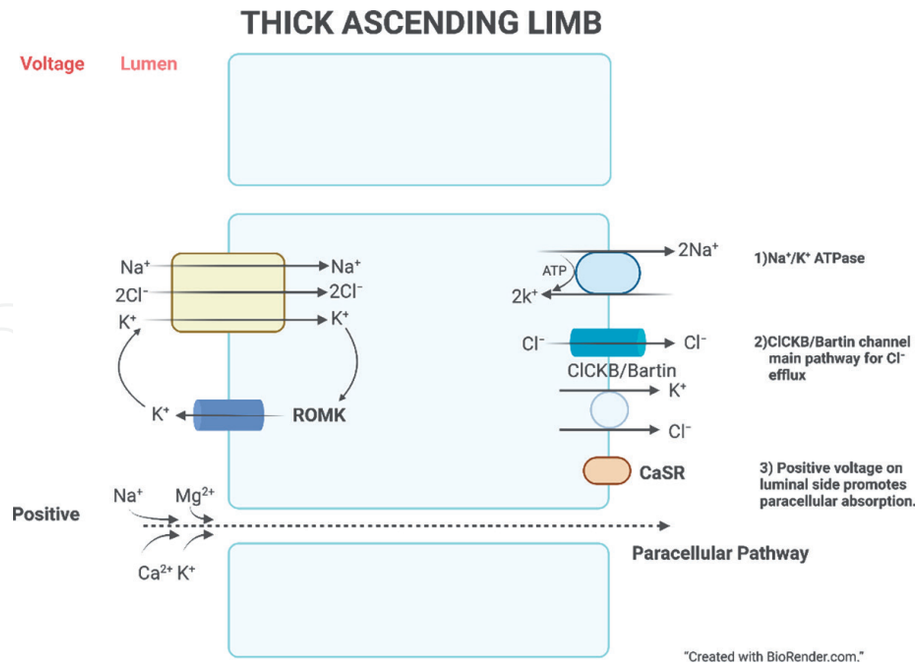

Figure 4.
Potassium handling in the thick ascending limb.

In principal cells, K^+ movement out of the cell into the tubular lumen is due to the electrochemical gradient generated by the entry of Na^+ into the cell *via* the ENaC channel located on the luminal side. The Na^+/K^+-ATPase pump at the basolateral membrane moves 3 Na^+ out of the cells in exchange for 2 K^+ creating a favorable concentration gradient. The gradient leads to the movement of Na^+ from the tubular lumen into the cell. This movement creates a negative voltage on the luminal side. This electrochemical gradient favors K^+ secretion into the lumen. It also promotes paracellular reabsorption of chloride (**Figure 5**) [27].

Intercalated cells are of two types, type A and type B, involved in acid-base regulation. In type A cells, the H^+/K^+ATPase pump on the luminal side results in

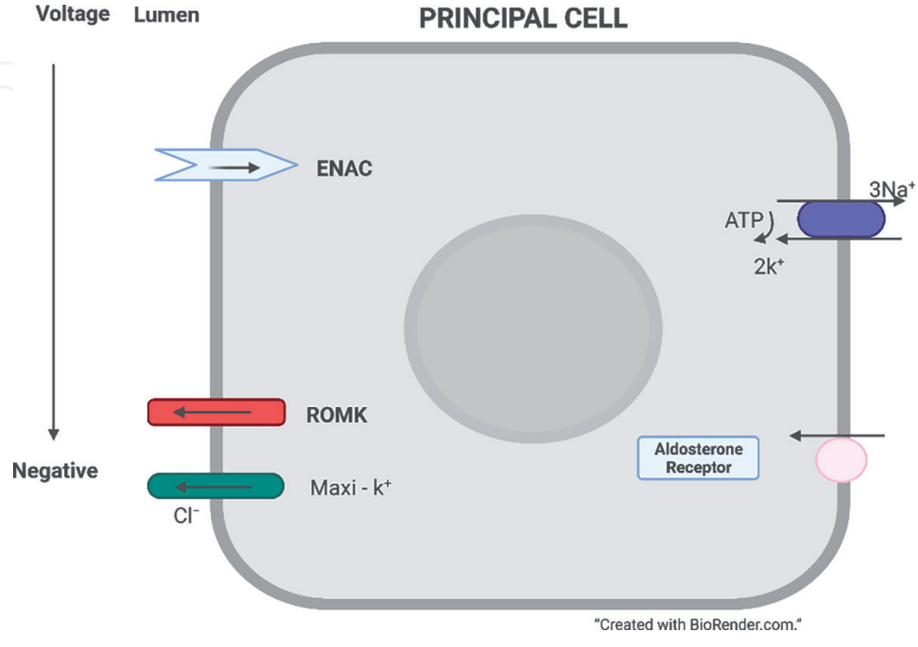

Figure 5.
Potassium handling in principal cells.

H+ secretion and K+ reabsorption (**Figure 6**) [28, 29]. The activity of this pump is increased in K^+-depleted states and decreased in the setting of elevated K^+ levels.

In intercalated type B cells, the reabsorption of K^+ is along with the Cl^- reabsorption *via* Cl^-/HCO_3^- exchanger, which is a proposed mechanism and not yet substantially proven (**Figure 7**) [29–31].

2.3 Role of aldosterone in potassium homeostasis

Aldosterone is a steroid hormone. It enters the cell, binds with a cytosolic receptor and moves to the nucleus, increasing the synthesis of sgk mRNA (serum and glucocorticoid regulated kinase messenger ribonucleic acid), resulting in sgk protein [32].

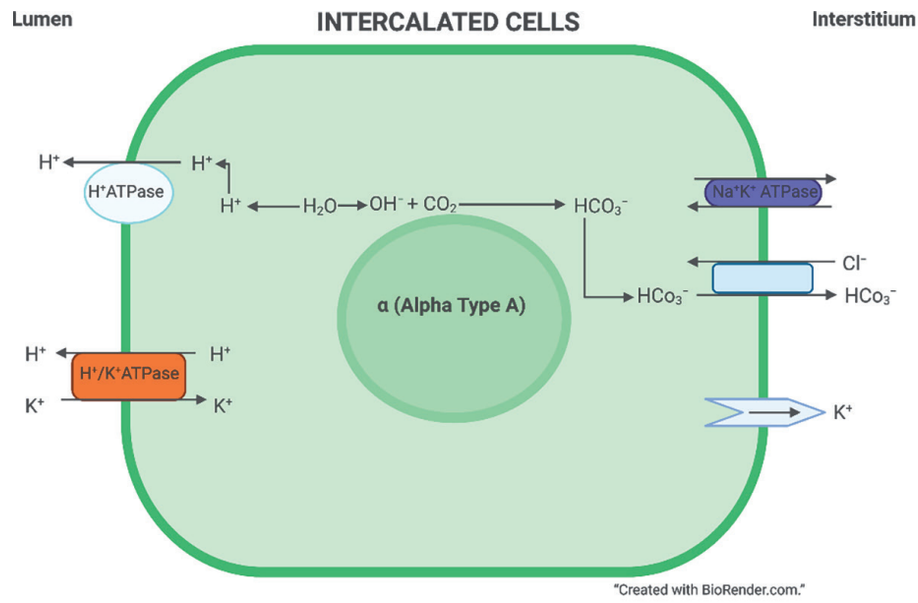

Figure 6.
Potassium handling in intercalated type A cell.

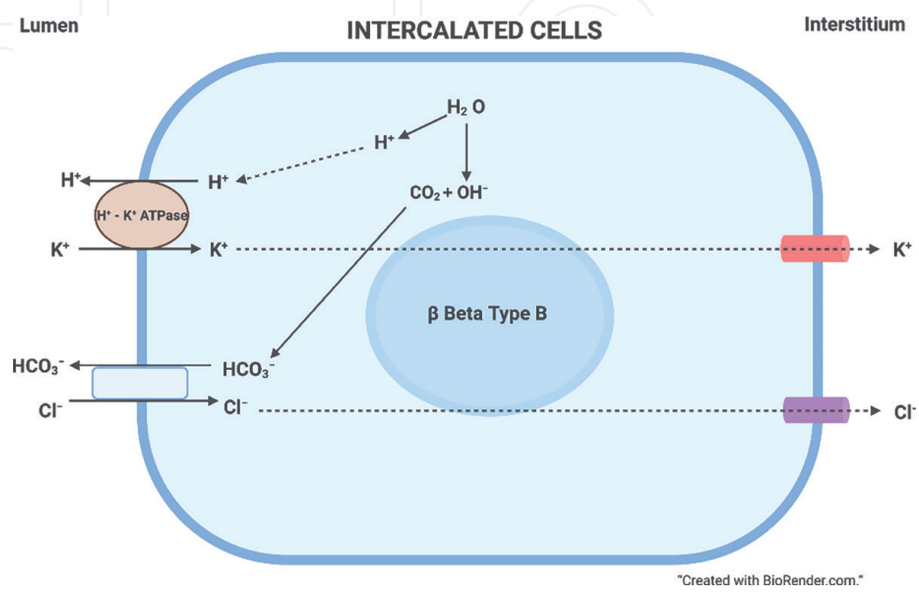

Figure 7.
Potassium handling in intercalated type B cell.

sgk protein stimulates the ENaC activity sevenfold. An increase in serum K^+ levels as little as 0.1–0.2 mEq/L can stimulate significant aldosterone levels [33].

2.4 Tubular flow and potassium secretion

Increasing the distal tubular flow rate potentiates K^+ secretion in those segments. This effect is more prominent when a person consumes a high K^+ diet as it also causes a simultaneous increase in aldosterone levels. Under normal circumstances, the fluid entering the distal tubule has a K^+ concentration of <1 mEq/L as most of the K^+ filtered is absorbed in the earlier parts of the nephron. Due to water reabsorption in the presence of ADH (antidiuretic hormone) and K^+ secretion in the tube's distal parts, the tubular K^+ concentration increases. However, if the distal flow rate is increased, enhanced flow washes the secreted K^+, keeping the K^+ concentration in the tubular fluid relatively lower and creating a favorable concentration gradient for K^+ secretion [34, 35].

Increased distal flow also increases Na^+ delivery to the distal nephron, increasing Na entry into the cells and potentiating the changes to create a favorable electrochemical gradient for K^+ secretion.

Two major K^+ channels are found in the thick ascending loop, DCT, cortical, and medullary collecting ducts. ROMK, also known as the constitutive K^+ secretary channel, is responsible for K^+ secretion during normal tubular flow. Cortical ROMK expression is upregulated by aldosterone and increased plasma K^+ concentration, whereas medullary ROMK expression is regulated by plasma K^+ levels and not aldosterone.

BK channels are also known as big/large conductance channels or "Maxi K" channels opened by the high tubular flow, hence were earlier called a flow-dependent channel. High tubular flow increases Na^+ delivery and eventually causes apical membrane depolarization. The depolarization leads to increased intracellular calcium levels and activates the BK channels. Recent studies suggest that K^+ secretion by ROMK is also increased in the setting of increased tubular flow. Both these channels work together in maintaining potassium homeostasis and preventing hyperkalemia. Either of them is upregulated in the absence of the other channel [36].

2.5 Role of the colon in potassium homeostasis

The primary absorption site for K^+ from the diet is the small intestine. The colon plays a minimal role in the absorption and secretion of potassium. Potassium secretion occurs primarily by passive mechanisms; however, in the rectum and sigmoid colon, K^+ is secreted by an active process [37].

Animal studies have shown that active K^+ secretion is mediated by apical K^+ channels, which coordinate with the basolateral $Na^+/K^+/Cl^-$ co-transporter. Intermediate conductance K^+ (IK) and large-conductance K^+ (BK) channels are present on the apical membrane of colonic epithelia. In patients with chronic renal insufficiency, especially when creatinine clearance is less than 10 mL/min, the net colonic K^+ secretion increases compared to normal renal function due to increased expression and activity of the BK channel. Colonic K^+ losses increase in the setting of diarrhea and by using cation resins (e.g., sodium polystyrene sulfonate) [38].

2.6 Feedforward control of potassium balance

Feedforward control means the response to a specific signal is preset and happens irrespective of the changes in the environment, unlike in the feedback mechanism where the changes in the environment control the pathway.

An increase in dietary intake of K^+ causes an increase in renal excretion of potassium, even though the K^+ concentration is not sufficient to cause any changes in plasma K^+ concentration or stimulate aldosterone. It was also noted that this mechanism acts independently and is not altered by changing the tubular flow rate of urine, urine pH, renal Na^+ excretion, or an aldosterone antagonist. `The feedforward mechanism is wholly dissociated from the common pathways involved in the feedback mechanisms of K^+ homeostasis [39].

The precise mechanism is still unknown, but it is hypothesized that there is a possible gastrointestinal-renal signaling pathway in humans responsible for this feedforward control of K^+ homeostasis [40].

2.7 Circadian rhythm and potassium levels

Potassium excretion is also influenced by the circadian rhythm irrespective of the activity levels or posture. The peak potassium excretion is observed in the middle of the day [41]. The presence of an oscillator system in DCT, connecting tubule and cortical collecting duct renal tubular cells, is responsible for the circadian variation of potassium excretion. The pathway includes cellular receptors for central nervous system signals, intracellular messenger's, effectors, and renal tubule membrane transporters [42]. The oscillations result in circadian gene and transcriptional factor expression changes modifying the expression of vasopressin V2 receptor and multiple transcellular channels (Aquaporin 2, Aquaporin 4, alpha ENaC, and ROMK-1), maintaining the plasma sodium and potassium concentration [39, 43]. ROMK gene expression is higher during physical activity, whereas the H^+/K^+ATPase gene expression is higher at rest [44]. Circadian rhythm causes a variation in aldosterone secretion, thus impacting renal potassium excretion [45].

3. Conclusion

To maintain a normal potassium concentration, both the feedback and feedforward mechanisms work in tandem. After a potassium-rich diet, the increased plasma potassium levels gain entry into the cells *via* transcellular processes. At the same time, the body gears up to activate the renal and the colonic potassium excretion. This is the classical feedback pathway, whereas the feedforward pathway acts independently. Understanding the intricate mechanisms of potassium homeostasis in humans is a must in our clinical approach to potassium disorders for effective treatment strategies.

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Conflict of interest

We declare no conflict of interest.

Notes/thanks/other declarations

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Acronyms and abbreviations

K^+	potassium
mEq/L	milliequivalent/liter
kg	kilogram
DNA	deoxyribonucleic acid
ICF	intracellular fluid
ECF	extracellular fluid
Na^+/K^+-ATPase	sodium/potassium-adenosine triphosphatase
Na^+	sodium
GLUT4	glucose transporter type 4
ATP	adenosine triphosphate
Cl^-	chloride
pH	a scale used to specify the acidity or basicity of an aqueous solution
H^+	hydrogen
MCT	monocarbohydrate transporter
NHE1	sodium hydrogen exchanger 1
PCT	proximal convoluted tubule
Ca^{2+}	calcium
$Na^+/K^+/Cl^-$ co-transporter	sodium/potassium/chloride co-transporter
ROMK	renal outer medullary potassium channel
DCT	distal-convoluted tubule
ENaC	epithelial sodium channel
H^+/K^+ATPase	hydrogen/potassium adenosine triphosphatase
Cl^-/HCO_3^- exchanger	chloride/bicarbonate exchanger
mRNA	messenger ribonucleic acid
ADH	antidiuretic hormone
BK/Maxi K channels	big/large conductance channels
IK	intermediate conductance

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Author details

Shakuntala S. Patil* and Sachin M. Patil
University of Missouri, Columbia, MO, USA

*Address all correspondence to: drshaku123@outlook.com

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