

Renal Potassium Homeostasis

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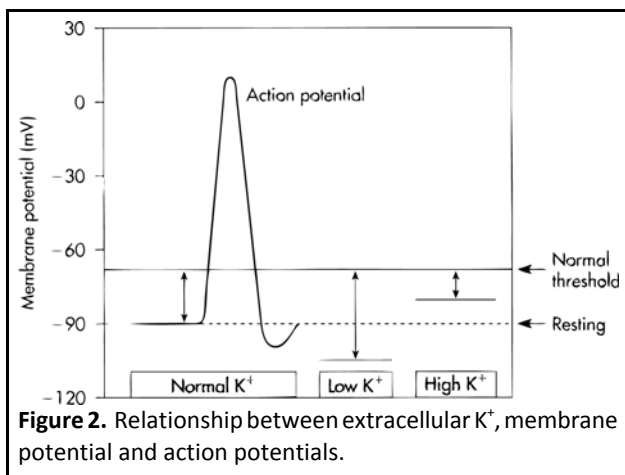
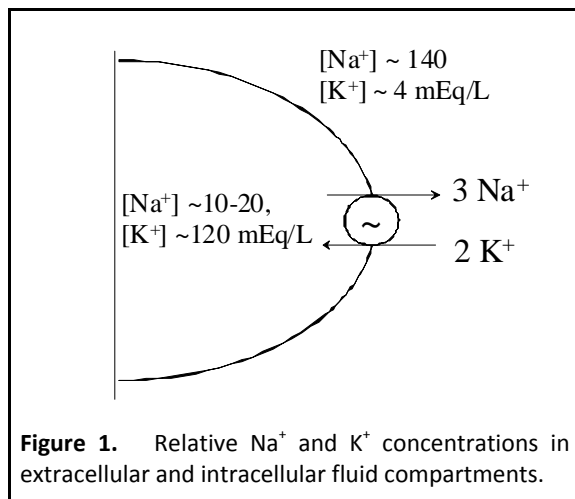
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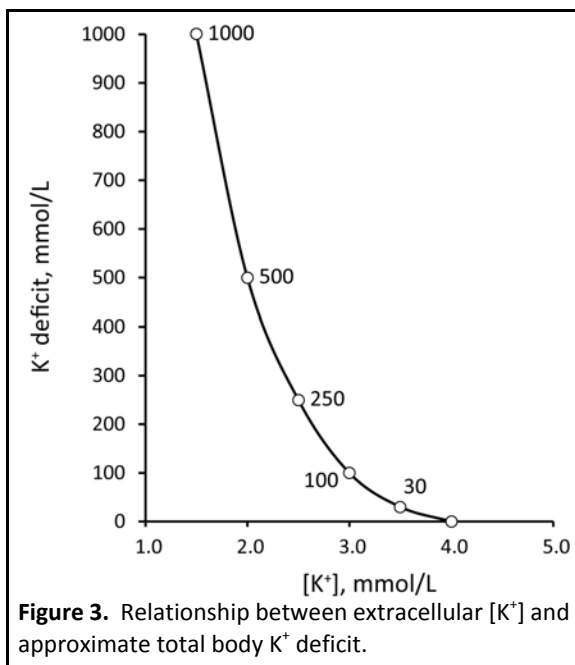
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Potassium is an essential mineral, present in all body fluids, both intracellular and extracellular, and for which abnormal concentrations result in substantial clinical disorders. Potassium deficiency leads to decreased insulin sensitivity, which can worsen diabetes mellitus, hypertension, decreased renal sodium excretion and increased susceptibility of the heart to the potentially fatal ventricular arrhythmias. Excessive extracellular potassium concentrations leads to muscle weakness and, eventually to lethal ventricular arrhythmias. Death by lethal injection uses an acute potassium overdose that causes the heart to “stop beating.”

The majority of total body potassium is in the intracellular compartment. This is because of the $\text{Na}^+\text{-K}^+\text{-ATPase}$ that is present in almost all cells and drives cellular K^+ uptake (Figure 1). The transmembrane K^+ gradient is the primary determinant of membrane voltage. Membrane voltage is important for both excitable (Figure 2) and non-excitabile cells, the body “works hard” to maintain the intracellular-to-extracellular K^+ gradient as constant as possible. As a result, when there is chronic K^+ deficiency the body shifts K^+ from intracellular to extracellular compartments.



This is important because potassium is commonly measured in the extracellular fluid compartment, not in the intracellular compartment. Consequently, potassium deficiency cannot be estimated from the change in extracellular potassium concentration multiplied by either plasma volume or even total body water. The relationship between hypokalemia and total body K^+ deficit is almost exponential (Figure 3).



Potassium homeostasis reflects a balance between intake and excretion. Figure 4 summarizes the balance between intake and excretion and the relative amounts of potassium in cellular stores (intracellular fluid) and extracellular fluid.

Since the majority of potassium is present in the intracellular compartment, redistribution of potassium between the intracellular and extracellular compartments can be very important. Changes in K^+ 's distribution between intracellular and extracellular compartments is the primary short-term response to changes in K^+ availability.

In particular, insulin and beta-adrenergic agonists stimulate $Na^+-K^+-ATPase$, increasing cellular K^+ uptake and decreasing extracellular K^+ . Insulin's effect on K^+ uptake occurs through different mechanisms than its effect on glucose uptake. Increased extracellular osmolality if due to compounds that cannot cross the plasma membrane causes potassium to shift out of cells into the extracellular fluid compartment, resulting in hyperkalemia. Aldosterone has long-term effects to stimulate $Na^+-K^+-ATPase$ and thereby increase potassium movement from extracellular sites into cells. Finally, a putative GI tract hormone likely regulates cellular K^+ uptake, because oral K^+ is much more rapidly shifted into intracellular compartments than is intravenous K^+ .

The primary long-term regulation of potassium homeostasis is renal potassium excretion. In contrast to many of the other ions which the kidney regulates, renal potassium excretion follows a different paradigm. Although potassium is freely filtered at the glomerulus and there is reabsorption in the proximal tubule and the loop of Henle, neither of these processes regulate renal potassium excretion.

Almost all regulation of renal potassium excretion occurs in the collecting duct, where there are parallel mechanisms to secrete and to reabsorb potassium. Moreover, potassium secretion and reabsorption occur in two different cell types in the collecting duct. Under most

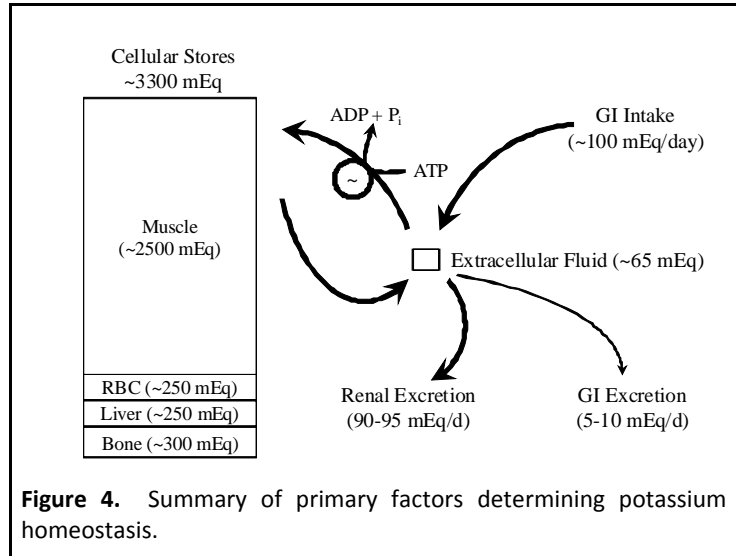


Figure 4. Summary of primary factors determining potassium homeostasis.

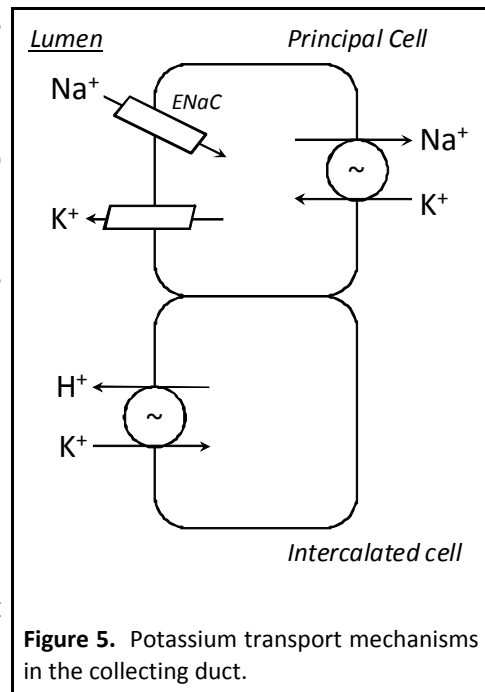


Figure 5. Potassium transport mechanisms in the collecting duct.

conditions, the collecting duct needs to secrete potassium in order to excrete the potassium that is ingested in foods.

Collecting duct principal cells secrete K^+ into the urine. Sodium is absorbed from the luminal fluid (nascent urine) via the epithelial Na^+ channel, ENaC. The sodium is excreted across the basolateral membrane via $Na^+-K^+-ATPase$, which brings K^+ into the cell and increases the intracellular K^+ concentration. K^+ then exits the cell across the apical membrane via an apical K^+ channel (Figure 5). Blocking Na^+ absorption blocks K^+ secretion.

Intercalated cells are less numerous than principal cells and their primary role is in acid-base homeostasis. However, they have an apical $H^+-K^+-ATPase$ which hydrolyzes ATP to energize K^+ absorption from the luminal fluid in exchange for H^+ secretion. The potassium then exits the cell via a basolateral potassium channel (not shown in the figure). This enables intercalated cells to mediate an important role in potassium homeostasis in states of potassium depletion.

The relative contributions of principal cell-mediated potassium secretion and intercalated cell-mediated potassium reabsorption determines the net potassium transport.

It is important to emphasize that although glomerular filtration is not an important mechanism in renal potassium excretion, the kidney's maximal rate of potassium excretion parallels overall kidney function, which parallels the glomerular filtration rate. Thus, people with decreased kidney function have a decreased ability to secrete potassium and are more susceptible to developing hyperkalemia.

Renal potassium transport is regulated by a variety of mechanisms. Changes in extracellular potassium, completely by itself, regulates renal potassium transport. Aldosterone is the most important hormonal regulatory mechanism. Aldosterone increases expression and activity of both the apical sodium channel, ENaC, and the basolateral $Na^+-K^+-ATPase$, and thereby increases renal potassium excretion. It also increases extrarenal $Na^+-K^+-ATPase$, which increases extra-renal cellular potassium uptake, further reducing extracellular potassium concentrations. Anything that increases sodium delivery to the collecting duct results in increased sodium absorption by principal cells, which results in increased principal cell-mediated potassium secretion.

The renal response to increase potassium excretion involves prostaglandin production in order to coordinate apical and basolateral potassium transport mechanisms. Patients using inhibitors of prostaglandin formation, non-steroidal anti-inflammatory drugs, have increased likelihood of developing hyperkalemia, particularly if they have concomitant kidney disease.

There is also a small component of potassium excretion that occurs in the colon. However, the amount is generally small, ~ 10 mEq per day, and although it can increase in hyperkalemia or in patients with chronic kidney disease, it quantitatively is a less important mechanism of long-term potassium homeostasis.