PHYSIOLOGY OF K⁺ BALANCE

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This is an exercise involving the integration of a case presentation of diuretic-induced hypokalemia with the physiology of K⁺ balance. Students are presented with a case presentation involving the development and correction of diuretic-induced hypokalemia. K⁺ homeostasis, including the distribution of K⁺ in the body and total body K⁺ balance, is summarized. The renal handling of K⁺, including the filtered load, reabsorption by proximal segments of the nephron, and secretion by distal segments of the nephron, is outlined. The mechanisms for the control of the secretion of K⁺ are discussed. Finally, an exercise involving integration of the case presentation with the physiology of K⁺ balance is presented. This exercise works well in an interactive session with students. The exercise has proved highly useful in the presentation and understanding of basic concepts involved in the physiology of K⁺ balance.


Key words: renal potassium handling; hypokalemia

An exercise concerning the physiology of K⁺ balance has been used and refined as part of the first-year curriculum in the Mayo Medical School. The exercise incorporates three major components: a case presentation of a common clinical problem, total body K⁺ balance, and the renal handling of K⁺. The students extract data from each of these three elements to complete the exercise. The exercise is presented without the answers so that the table at the conclusion of the exercise can be used in an interactive fashion with students. Student feedback on this exercise has been very positive, with students commenting that “working with the numbers helped with an understanding of the concepts.”

EXERCISE: INTEGRATION OF A CASE PRESENTATION OF DIURETIC-INDUCED HYPOKALEMIA WITH THE PHYSIOLOGY OF K⁺ BALANCE

The objective of this exercise is to apply the basic principles of the physiology of K⁺ balance to a case presentation describing the development and correction of diuretic-induced hypokalemia.

Case presentation: Diuretic-induced hypokalemia. A middle-aged man who weighed 20 lb over his ideal weight presented blood pressure elevated to 160/110 mmHg. He had no cardiovascular complications of hypertension and normal levels of serum creatinine and K⁺ (4 meq/l). Hydrochlorothiazide (a diuretic that decreases Na⁺ reabsorption in the distal nephron) at 25 mg twice daily was prescribed, with advice to return for reexamination in 1 mo.

He returned 1 mo later complaining of muscle cramps, frequent nighttime urination, and general weakness. His blood pressure was 150/90 mmHg, and the serum creatinine was still normal. However, the serum K⁺ concentration had decreased to 3.0 meq/l. A 24-h urine specimen contained 256 meq of Na⁺. Because the urinary excretion of Na⁺ usually approximates the dietary intake, it was concluded that he was ingesting excessive Na⁺. A nutritionist instructed the patient in
a 90-meq Na\(^+\) diet with weight-reduction features. The hydrochlorothiazide was continued, but both 25-mg tablets were now to be taken in the morning, with none being taken at bedtime.

One month later, the patient's blood pressure was 130/90 mmHg, he had lost 8 lb, and the serum K\(^+\) concentration was 4.0 meq/l. He was urinating only once or twice during the night, and the cramps in his legs were no longer troublesome.

**K\(^+\) HOMEOSTASIS**

K\(^+\) is the major intracellular cation (1). A high level within cells is important for the optimal operation of many enzymatic processes and the control of cell volume. In addition, the establishment of a K\(^+\) concentration ([K\(^+\)]) difference across the plasma membrane of the cell is important for the normal function of excitable tissues.

The extracellular fluid [K\(^+\)] is a function of the total body K\(^+\) content and the relative distribution of K\(^+\) between the extracellular and intracellular fluid compartments. The total body K\(^+\) content depends on both the dietary intake of K\(^+\) and its excretion from the body.

**DISTRIBUTION OF K\(^+\) IN THE BODY**

Virtually all K\(^+\) within the body is contained inside cells, with only 2% being located in the extracellular fluid space. The distribution of K\(^+\) within the body is summarized in Fig. 1.

In the steady state, the intake of K\(^+\) into the body must be matched by its excretion, a process occurring primarily via the kidneys. However, the renal responses to fluctuations in K\(^+\) intake are not immediate, and it takes several hours or even days for appropriate adjustments in K\(^+\) excretion to occur. Wide fluctuations in the [K\(^+\)] of the extracellular fluid are prevented during the "lag period" by shifts of K\(^+\) between the intracellular and extracellular compartments (extrarenal K\(^+\) homeostasis).

The extrarenal handling of K\(^+\) is essential for the maintenance of plasma [K\(^+\)] within a narrow range. This is especially true during situations in which the body is challenged with an acute load of K\(^+\). Thus,
with an acute K⁺ load (dietary or otherwise), K⁺ is rapidly taken up into cells (liver, skeletal muscle, adipose tissue). This prevents a large rise in plasma [K⁺]. Over the next several hours K⁺ is slowly released from these storage sites and excreted by the kidneys.

With potassium depletion, which occurs with diuretic therapy, the losses from the extracellular fluid are not fully compensated for by shifts from the tissue stores. A decrease in the plasma K⁺ from 4 to 3 meq/l corresponds to an ~300-meq K⁺ deficit as determined empirically (Fig. 2) (2). Note that if the loss of K⁺ from the plasma were proportionate to the loss of total body K⁺, it would equal a total body K⁺ deficit of 1,000 meq.

**RENAK EXCRETION**

The kidney can vary the amount of K⁺ excreted in the urine over a wide range. The kidney is able to excrete large amounts of K⁺. Accordingly, with normal renal function and even in the face of a large dietary K⁺ intake, significant hyperkalemia is rarely seen. In contrast, the kidney is less well able to conserve K⁺ (fractional K⁺ excretion can be reduced to ~2% of the filtered load). Thus K⁺ depletion and hypokalemia can result if K⁺ intake is restricted.

The process of renal K⁺ excretion involves two general steps. First, 90% of the filtered load of K⁺ is reabsorbed. This occurs in the proximal tubule and the loop of Henle. Second, K⁺ is secreted into the tubular fluid by the terminal portion of the distal convoluted tubule and the cortical portion of the collecting duct. These general aspects of renal K⁺ handling are summarized in Fig. 3.

Note that ~90% of the filtered load of K⁺ is reabsorbed before the K⁺ secretory site. The amount of K⁺ appearing in the urine reflects in large part the secretion of K⁺ at the distal secretory sites. Several factors have been identified as important regulators of K⁺ secretion and will be considered in detail below.

**REABSORPTION OF FILTERED K⁺**

**Glomerulus.** K⁺ is a small cation and is not bound in any appreciable amount to plasma protein. As a result, the K⁺ in the glomerular filtrate is essentially the same as in the plasma water. The filtered load of K⁺ is then plasma [K⁺] (4.0 meq/l) multiplied by the glomerular filtration rate (180 l/day), or 720 meq/day.

**Proximal tubule.** The proximal tubule (convoluted and straight) reabsorbs roughly 80% of the filtered load of K⁺. This fraction remains relatively constant under most conditions. Thus the proximal tubule does not normally contribute significantly to the regulation of urinary K⁺ excretion.
The reabsorption of K\(^+\) by the proximal tubule probably involves both passive and active mechanisms. Under most conditions, K\(^+\) reabsorption is proportional to the amount of NaCl and fluid reabsorbed.

**Loop of Henle.** Approximately 10% of the filtered load of K\(^+\) is reabsorbed by the thick ascending limb of Henle's loop. Under normal conditions, the reabsorption of K\(^+\) is relatively constant, although this segment does have the capacity to increase K\(^+\) absorption in response to an increased load.

**SECRETION OF K\(^+\)**

**Distal tubule and collecting duct.** It is the distal convoluted tubule and the cortical portion of the collecting duct that primarily determine the amount of K\(^+\) appearing in the urine. The more terminal portions of the collecting duct can affect minor adjustments in urinary K\(^+\) excretion.

Under most conditions (normal western diet), K\(^+\) is secreted at these sites. However, with K\(^+\) depletion, reabsorption of K\(^+\) occurs. These two transport mechanisms are located in separate cells. The secretory cell is the “principal cell,” whereas the “intercalated cell” is the cell responsible for K\(^+\) reabsorption.

K\(^+\) secretion occurs by a two-step process. First, K\(^+\) is brought into the cell across the basolateral cell membrane (Na\(^+\)-K\(^+\)-ATPase). Some K\(^+\) recycles across this membrane, but a portion enters the tubule lumen by passive diffusion across the apical cell membrane. The amount of K\(^+\) that either recycles back to the blood across the basolateral cell membrane or enters the tubule lumen is determined by the permeability of each membrane to K\(^+\) and the respective electrochemical gradients for K\(^+\). Normally, the apical cell membrane is more permeable to K\(^+\). In addition, as shown in Fig. 4, the electrical profile across the cell favors luminal K\(^+\) entry.

**REGULATION OF K\(^+\) EXCRETION**

To understand the regulation of renal K\(^+\) excretion, it is important to focus on the secretion of K\(^+\) by the terminal portion of the distal convoluted tubule and the cortical portion of the collecting duct (K\(^+\) secretory site). Several factors act at this site to regulate K\(^+\) secretion and thereby K\(^+\) excretion.

**Dietary K\(^+\).** Urinary K\(^+\) excretion parallels dietary intake. With dietary K\(^+\) loading, K\(^+\) secretion is enhanced. This is the result of increased uptake of K\(^+\) into cells (via Na\(^+\)-K\(^+\)-ATPase) and is largely the result of changes in mineralocorticoid hormone levels (see Hormones). Conversely, cellular uptake of K\(^+\) is reduced with K\(^+\) depletion, again in response to changes in mineralocorticoid hormone levels.

**Plasma K\(^+\).** As plasma K\(^+\) is increased, K\(^+\) secretion also increases, reaching a plateau at a plasma [K\(^+\)] of ~6 meq/l. Because increases in plasma [K\(^+\)] stimulate aldosterone secretion, the increased K\(^+\) secretion can be attributed in part to mineralocorticoid-induced uptake of K\(^+\) into the K\(^+\) secretory cells. In addition, elevated plasma [K\(^+\)] would also be expected to reduce the passive component of K\(^+\) recycling across the basolateral cell membrane. Together, these effects increase K\(^+\) excretion.

**Hormones.** The most important hormone regulating K\(^+\) secretion by the terminal portion of the distal convoluted tubule and the cortical portion of the collecting duct is aldosterone. Aldosterone stimulates K\(^+\) secretion by increasing cellular uptake of K\(^+\) via the Na\(^+\)-K\(^+\)-ATPase and by increasing the K\(^+\) permeability of the apical cell membrane of the K\(^+\) secretory
cells. Aldosterone also stimulates Na\(^+\) reabsorption by these nephron segments. This, in turn, increases the transepithelial potential difference and further stimulates K\(^+\) secretion.

**Luminal flow rate.** As the flow of tubular fluid past the K\(^+\) secretory site is increased, K\(^+\) secretion is increased. This flow-related increase in K\(^+\) secretion is thought to result from the maintenance of a favorable cell-to-lumen concentration gradient for K\(^+\). Because the amount of K\(^+\) secreted into the tubule lumen will be limited by this gradient, a fast flow rate (decreased contact time) will prevent luminal K\(^+\) from rising to levels that would subsequently limit further K\(^+\) secretion.

**EFFECTS OF DIURETICS ON K\(^+\) EXCRETION**

Diuretics commonly increase renal K\(^+\) excretion. Those diuretics that have their site of action proximal to the K\(^+\) secretory site will increase urinary K\(^+\) loss (e.g., osmotic diuretics, carbonic anhydrase inhibitors, loop diuretics, and thiazides). The increased K\(^+\) secretion results from the diuretic-induced increase in luminal fluid flow rate and delivery of Na\(^+\). In addition, the loop diuretics inhibit K\(^+\) reabsorption by the thick ascending limb. The K\(^+\)-sparing diuretics (spironolactone, triamterene, and amiloride) prevent K\(^+\) loss in the urine through inhibition of its secretion.

**DISCUSSION**

At the initial presentation, the dietary intake of K\(^+\) is 100 meq of K\(^+\) per day as derived from Fig. 1. The excretion of K\(^+\) is 90 meq/day, also as derived from Fig. 1. The plasma K\(^+\) is 4 meq/l as derived from both the case presentation and the syllabus. The total body K\(^+\) is 3,500 meq as derived from the information in Fig. 1, including both tissue stores and extracellular fluid. The filtered K\(^+\) is 720 meq/day (as derived from the syllabus), where the filtered load is equal to 4 meq/l \(\times\) 180 l/day. The reabsorbed K\(^+\) is equal to 90% of the filtered load shown in Fig. 3. The distal delivery is simply the filtered minus reabsorbed K\(^+\) at 72 meq/day. The distal secretion, therefore, is the excreted K\(^+\) (90 meq/day) minus the delivered K\(^+\) (72 meq/day), which is 18 meq/day.
At the 1-mo visit, the K\(^{+}\) intake continues at 100 meq/day. The excretion can be calculated from the K\(^{+}\) loss. The plasma K\(^{+}\) concentration is 3 meq/l as obtained from the case presentation. This results from a decrease in total body K\(^{+}\) of 300 meq as obtained from the information in Fig. 2. A 300-meq loss over a 30-day period represents a 10 meq/day increase in K\(^{+}\) excretion over the initial 90 meq/day. Thus the K\(^{+}\) excretion at the 1-mo visit has averaged 100 meq/day. The filtered K\(^{+}\) is now 540 meq/day, and the reabsorbed K\(^{+}\) is 486 meq/day. The distal delivery is 54 meq/day, and, because the excretion is 100 meq/day, the distal secretion is 46 meq/day.

At 2 mo, this process is reversed. The K\(^{+}\) intake remains 100 meq/day, the excretion is calculated to be 80 meq/day, and the distal secretion now becomes 8 meq/day. Thus this exercise described the major role of distal secretion in determining final urinary excretion. In addition, it shows the marked effect of changes in Na\(^{+}\) intake on the renal handling of K\(^{+}\) in diuretic therapy. The high Na\(^{+}\) intake leads to increased delivery of Na\(^{+}\) and water to the distal nephron, where the luminal flow rate is further increased by the diuretic and leads to increased K\(^{+}\) secretion. The low Na\(^{+}\) intake reduces the delivery of Na\(^{+}\) and water to the distal nephron so that the effect of the diuretic on K\(^{+}\) secretion is offset and K\(^{+}\) balance is restored.

The case presentation is taken from an actual clinical case. However, the presentation has been simplified by having the low-Na\(^{+}\) diet completely correct the hypokalemia. In the original case, the low-Na\(^{+}\) diet partially corrected the hypokalemia with a final serum K\(^{+}\) concentration of 3.5 meq/l. The simplification allows for a symmetrical calculation of the changes in distal K\(^{+}\) secretion. The exercise, of course, can be performed with the incomplete correction of the hypokalemia; however, this tends to complicate the calculations and interfere with the presentation of the basic principles.

A second simplification involves the attribution of the entire correction of the hypokalemia to changes in distal K\(^{+}\) secretion. In the presence of K\(^{+}\) conservation, reabsorption of K\(^{+}\) may also occur in the distal nephron segments. These two points can be brought out in the context of the discussion of Table 2 at the conclusion of the exercise. The exercise has been found to be useful in presenting and utilizing basic concepts involved in the physiology of K\(^{+}\) balance.

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References