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# Role of Muscle in Regulating Extracellular [$K^+$]

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**There is a positive association between diets rich in potassium, control of blood pressure, and prevention of stroke. Extracellular [$K^+$] is regulated closely to maintain normal membrane excitability by the concerted regulatory responses of muscle and kidney. Although kidney is responsible for ultimately matching $K^+$ output to $K^+$ intake each day, muscle contains more than 90% of the body's $K^+$ and can buffer changes in extracellular fluid [$K^+$] by either acutely taking up extracellular fluid $K^+$ or releasing intracellular fluid $K^+$ from muscle. It long has been assumed that the changes in muscle $K^+$ transport are a function of sodium pump (Na,K-adenosine triphosphatase [Na, K-ATPasell]) abundance, especially that of the $\alpha$2 isoform, which predominates in skeletal muscle. To test the physiologic significance of changes in muscle Na,K-ATPase expression, we developed the $K^+$ clamp, which measures insulin-stimulated cellular $K^+$ uptake in vivo in the conscious rat. By using the $K^+$ clamp we discovered that significant insulin resistance to cell $K^+$ uptake occurs as follows: (1) early in $K^+$ deprivation before a decrease in muscle sodium pump pool size, and (2) during glucocorticoid treatment, which increases muscle Na,K-ATPase $\alpha$2 levels greater than 50%. We also discovered that adaptation of renal and extrarenal $K^+$ handling to altered $K^+$ balance often occurs without changes in plasma [$K^+$], supporting a feedforward mechanism involving $K^+$ sensing in the splanchnic bed and adjustment of $K^+$ handling. These findings establish the advantage of combining molecular analyses of Na,K-ATPase expression and activity with systems analyses of cellular $K^+$ uptake and excretion in vivo to reveal regulatory mechanisms operating to control $K^+$ homeostasis.**
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The recent Institute of Medicine project on "Dietary Reference Intakes for Electrolytes and Water"[1] reports that adults should consume at least 4.7 g of potassium per day to lower blood pressure, blunt the effects of sodium chloride, and reduce the risk for kidney stones and bone loss. The project also states that most American women consume no more than half of this recommended amount, and that men's intake is only moderately higher. In comparison, most Americans consume more than the tolerable upper limit for sodium consumption of 3.8 g.[1] There is a long-standing awareness of the positive association between diets rich in potassium and the control of blood pressure and prevention of stroke,[2-4] which is not surprising given the fact that potassium is the main intracellular cation and a key determinant of cell volume and nerve and muscle excitability. These properties are all dependent on the steep transmembrane $K^+$ gradient established by the ubiquitous sodium pump, Na,K-adenosine triphosphatase (ATPase). Sodium pump ATP hydrolysis fuels the coupled uphill transport of $K^+$ into the cell and $Na^+$ out of the cell. Extracellular [$K^+$] must be regulated closely (it usually is between 3.8-5 mmol/L) to maintain normal membrane excitability. This is accomplished by the concerted responses of kidneys, which matches $K^+$ excretion to $K^+$ intake by secreting or actively reabsorbing $K^+$[5-7] and muscle, which contains the major pool of $K^+$ and can regulate $K^+$ distribution between the intracellular fluid (ICF) and extracellular fluid (ECF) compartments (Fig. 1). This review focuses on recent in vivo studies examining the role of muscle Na,K-ATPase in potassium homeostasis. Because a recent comprehensive review of Na,K-ATPase regulation and skeletal muscle contractility is available,[8] this topic is not emphasized.

To show the importance of the interplay between kidney and muscle, consider the day-to-day challenges associated with potassium ingestion. Total ECF contains only about 70

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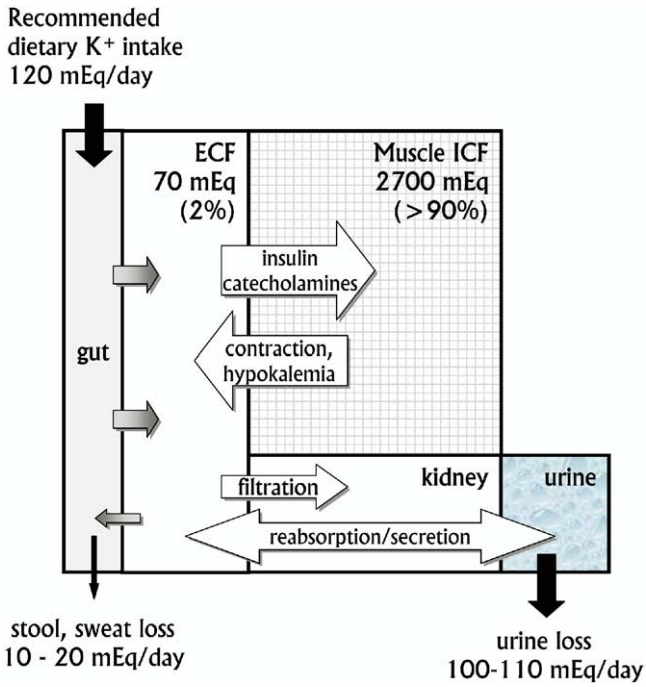


**Figure 1** Compartmental diagram of potassium homeostasis in an average person. More than 90% of the body's $K^+$ is located in the muscle ICF and only about 2% is located in the ECF. Regulation of $K^+$ transport by both muscle and kidneys leads to fine control of extracellular [$K^+$]. After a meal, the gut absorbs $K^+$ and postprandial insulin acutely increases cellular $K^+$ uptake into muscle (and liver, not shown). Muscular contraction continuously releases $K^+$ into the ECF, which either will be pumped back into the muscle or filtered into the kidney and excreted to balance intake. When $K^+$ intake is high or low there are a variety of regulatory responses. Both the kidney and the colon can secrete or reabsorb $K^+$ in a regulated fashion depending on whether $K^+$ intake is high or low. During hypokalemia the muscle exhibits an altruistic specialization to donate cell [$K^+$] to balance the discrepancy between $K^+$ input and output over time. When significant exercise causes hyperkalemia, catecholamines drive an increase in muscle cellular $K^+$ uptake. (Color version of figure is available online.)

mEq $K^+$, whereas the recommended dietary potassium intake from the Institute of Medicine is nearly twice this at 120 mEq/d (4.7 g/d/0.039 g/mEq) (Fig. 1). A large meal may contain 70 mEq $K^+$, which would be added to the ECF within a short time of its ingestion. ECF [$K^+$] would double if there were not rapid adjustments to either transfer the $K^+$ to the ICF compartment or excrete it. In fact, after a meal there is little change in ECF $K^+$ levels because postprandial insulin stimulates muscle and liver to actively take up both glucose and the $K^+$ not excreted in the short term by the kidneys.[9] Between meals, muscle activity releases $K^+$ into the ECF and, mysteriously, kidneys excrete an amount equal to the daily $K^+$ intake. In patients with end-stage renal disease, muscle serves as a buffer to sequester some of the dietary $K^+$ between dialysis sessions. During fasting or when consuming a low $K^+$ diet, the kidney adapts to reabsorb more and secrete less $K^+$ to the point that renal output decreases to near zero.[5,10] This occurs primarily as a result of adjustments in the distal nephron: a decrease in surface expression and an abundance of apical $K^+$ channels that mediate $K^+$ secretion[11,12] and an increase in apical H,K-ATPases that can mediate $K^+$ reabsorption.[13,14] Because $K^+$ loss in the stools and sweat persists during fasting and low $K^+$ diets, potassium must be redistributed continuously from ICF muscle stores to the ECF to prevent a drastic decrease in ECF [$K^+$]. That is, muscle exhibits an altruistic specialization to donate cell [$K^+$] to balance the discrepancy between $K^+$ input and output over time.[15-17] An impressive illustration of this regulatory response was shown by Knochel et al[18] in a study of soldiers in summertime basic training. Soldiers lost more than 40 mEq $K^+$/d in sweat alone. Hypokalemia did not develop because high muscle activity shifted $K^+$ into the ECF. Nonetheless, after 11 days of training, a total body $K^+$ deficit of more than 400 mEq developed, perhaps exacerbated by aldosterone secreted in response to daily bouts of dehydration.[18]

Active transport of $K^+$ by muscle Na,K-ATPase plays a central role in these scenarios of acute and chronic challenges to potassium homeostasis. This review focuses on the molecular mechanisms in place in muscle that contribute to potassium homeostasis, in particular, muscle-specific regulation of sodium pump isoforms, and a method we developed to assess cellular $K^+$ uptake in vivo.

## P-Type ATPases and $K^+$ Homeostasis

Potassium transport between the ECF and ICF is mediated by an array of transporters including P-type ATPases, cotransporters, and channels (shown in Fig. 2). Plasma membrane sodium pumps (Na,K-ATPase) actively transport $K^+$ from ECF into the cell and the renal hydrogen potassium pumps (H,K-ATPase) expressed during $K^+$-deficient states actively reabsorb $K^+$ from the renal tubular fluid back into the ECF.[14,19] These P-type ATPases are 1:1 heteromers of approximately 100-kd $\alpha$-catalytic subunits and approximately 50-kd $\beta$-glycoprotein subunits that share 65% homology. Cells also express $K^+$ cotransporters including bumetanide-sensitive sodium potassium 2 chloride transporters[20] and potassium 2 chloride transporters,[21] which can drive cellular $K^+$ uptake, but their roles in regulating ECF $K^+$ homeostasis have not been investigated. Multiple isoforms of sodium pump $\alpha$ and $\beta$ subunits exist and are expressed in a tissue-specific pattern.[13,14,19] Skeletal muscle expresses $\alpha$1,$\alpha$2, $\beta$1, and $\beta$2 isoforms. $\alpha$2 expression is fairly uniform across muscles, whether oxidative or glycolytic, but $\alpha$1 expression is twice as high in oxidative muscles such as soleus and diaphragm than in mixed or fast glycolytic muscles such as gastrocnemius and extensor digitorum longus.[22] Estimates place the percentage of $\alpha$2 protein at 40% to 60%.[16,23] $\beta$1 is expressed without $\beta$2 in soleus and diaphragm, and $\beta$2 is expressed without $\beta$1 in white gastrocnemius, and both are expressed in mixed fiber muscles.[22,24]

Differential expression suggests differential function, regulation, or subcellular distribution, and there is evidence for all of these in muscle. Studies in mice lacking one copy of $\alpha$1