Review Article

Kidney360

Extrarenal Effects of Aldosterone on Potassium Homeostasis

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Abstract

The role of aldosterone in regulating K^+ excretion in the distal nephron is well established in kidney physiology. In addition to effects on the kidney, aldosterone modulates K^+ and Na^+ transport in salivary fluid, sweat, airway epithelia, and colonic fluid. More controversial and less well defined is the role of aldosterone in determining the internal distribution of K^+ across cell membranes in nontransporting epithelia. *In vivo* studies have been limited by the difficulty in accurately measuring overall K^+ balance and factoring in both variability and secondary changes in acid-base balance, systemic hemodynamics, and other K^+-regulatory factors such as hormones and adrenergic activity. Despite these limitations, the aggregate data support a contributory role of aldosterone along with insulin and catecholamines in the normal physiologic regulation of internal K^+ distribution. The authors speculate differences in tissue sensitivity to aldosterone may also contribute to differential tissue response of cardiac and skeletal muscle to conditions of total body K^+ depletion.

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Introduction

The plasma potassium (K^+) concentration is maintained within a narrow range after ingestion of a K^+ load. This near constancy of plasma K^+ is somewhat surprising because K^+ is quickly absorbed by the gastrointestinal tract but the kidney excretes only one half of the load during the first 4–6 hours after ingestion. The ability to maintain normokalemia in this situation is due to several factors that dictate the distribution between the extracellular and intracellular compartments. These factors act to shift K^+ into the cell to allow enough time for the kidney to reestablish total body K^+ content. Were it not for these factors, ingestion of a typical meal could potentially double the extracellular K^+ concentration, producing life-threatening hyperkalemia because only 2% of total body K^+ (55–65 mEq) is found in the extracellular compartment. The degree to which plasma K^+ increases after a meal is dependent on the makeup of the diet, the magnitude of decreased kidney function, and the presence or absence of drugs that block the renin-angiotensin system (1). This review will focus on the normal physiologic factors that influence distribution of K^+ across the cell. The role of insulin and catecholamines in regulating the internal distribution of K^+ will be briefly discussed because these two factors play an important role in day-to-day physiology of K^+ homeostasis. A more extensive review of the literature will focus on the role played by aldosterone in maintaining the internal distribution of K^+. The role of pathologic conditions that alter K^+ distribution across the cell such as acid base disorders and changes in tonicity have been reviewed elsewhere and therefore will not be addressed (2,3).

Insulin

Postprandial release of insulin not only regulates the plasma glucose concentration, but also functions to shift dietary K^+ into cells (primarily skeletal muscle), providing a defense against hyperkalemia because adjustments in kidney K^+ excretion occur over several hours. After binding to cell surface receptors, insulin stimulates glucose uptake in responsive tissues through insertion of the glucose transporter protein GLUT4 (4). Activation of the receptor leads to increased cellular K^+ uptake by increasing the activity of the Na^+-K^+-ATPase pump. Increased pump activity is the result of translocation of the protein from intracellular stores to the cell membrane and increased cell Na^+ concentration resulting from stimulation of Na^+/H^+ exchanger (5) (Figure 1). In patients with metabolic syndrome, insulin resistance, or CKD, insulin-mediated glucose uptake is impaired, but cellular K^+ uptake remains normal, demonstrative of divergent intracellular pathways regulating insulin-mediated glucose and K^+ uptake after receptor binding (6).

Insulin levels increase two- to three-fold when infusion of KCl raises the plasma K^+ concentration by at least 1–1.5 mEq/L, leading to increased cellular uptake and correction of hyperkalemia (7,8). When basal levels of insulin are first reduced with infusion of somatostatin, modest K^+ loads produce hyperkalemia that can be prevented when insulin levels are restored to

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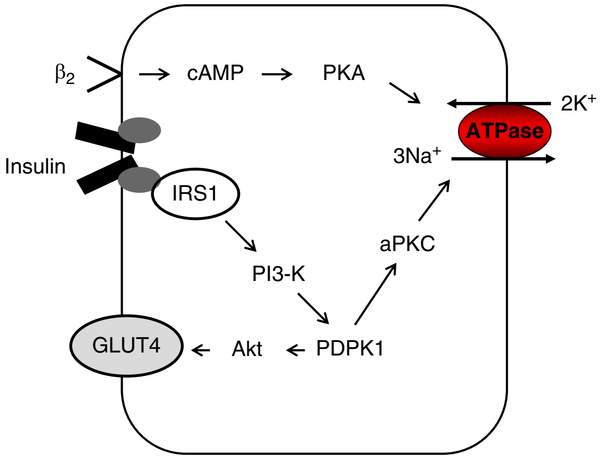

Figure 1. | Cell model illustrating β_2-adrenergic and insulin-mediated regulatory pathways for K^+ uptake in skeletal muscle. β_2-Adrenergic stimulation and insulin both lead to K^+ uptake by stimulating the activity of the Na^+-K^+-ATPase pump primarily in skeletal muscle, but they do so through different signaling pathways. β_2-Adrenergic stimulation leads to increased pump activity through a cAMP- and protein kinase A–dependent pathway. Insulin binding to its receptor leads to phosphorylation of the insulin receptor substrate protein (IRS-1), which in turns binds to phosphatidylinositide 3-kinase (PI3-K). The IRS/1-PI3-K interaction leads to activation of 3-phosphoinositide dependent protein kinase-1. The stimulatory effect of insulin on glucose uptake and K^+ uptake diverge at this point. A serine/threonine protein kinase–dependent pathway is responsible for membrane insertion of the glucose transporter protein GLUT4, whereas activation of atypical protein kinase C leads to membrane insertion of the Na^+-K^+-ATPase pump. Not shown is that insulin stimulates pump activity by increasing cell Na^+ brought about by a stimulatory effect on the Na^+-H^+ antiporter.

normal, suggesting even basal levels are essential to the maintenance of normal K^+ homeostasis (9). Insulin-stimulated cellular K^+ uptake is initially predominant in the liver and subsequently in skeletal muscle followed by adipose tissue (10) (Figure 2). Insulin is clinically utilized as a first-line therapy for emergent treatment of hyperkalemia, given the potency to shift K^+ into cells.

Catecholamines

Catecholamines play an important role in the regulation of internal K^+ distribution, with α-adrenergic receptors impairing and β-adrenergic receptors promoting cellular entry of K^+. These effects importantly regulate the cellular release of K^+ during exercise (11). With vigorous exercise, K^+ is released from the intracellular space and accumulates in the interstitial compartment, reaching concentrations as high as 10–12 mM. Interstitial K^+ accumulation elicits rapid vasodilation, allowing blood flow to perfuse exercising muscle (12). Accumulation of K^+ is also a factor limiting the excitability and contractile force of muscle, accounting for the development of fatigue (13,14). Although the mechanism is likely to be multifactorial, total-body K^+ depletion blunts the accumulation of K^+ into the interstitial space, limiting blood flow to skeletal muscle and accounting for the association of hypokalemia with rhabdomyolysis.

The activation of autonomic nerves and increases in circulating catecholamines acting through β_2 adrenergic receptors limit the rise in extracellular K^+ concentration during exercise. β_2-Receptor stimulation leads to generation of cyclic AMP and subsequent activation of the Na^+-K^+-ATPase pump, resulting in Na^+ efflux and K^+ influx (15) (Figure 1). This pathway is independent of insulin and explains the additive effect of insulin and epinephrine to shift K^+ into cells. After cessation of exercise, α-stimulation promotes K^+ exit from the cell minimizing development of hypokalemia due to persistent β_2-receptor stimulation from residual circulating catecholamines. These effects explain observations that propranolol exacerbates and prolongs the increase in K^+ during exercise, whereas α-blockade with phentolamine lowers the K^+ level during recovery. Increased afferent nerve activity originating in the diseased kidney of patients with ESKD contributes to increased sympathetic outflow and can exacerbate exercise and fasting-related hyperkalemia due to α-adrenergic receptor stimulation (16).

Aldosterone

Aldosterone is the major mineralocorticoid in humans and plays an important role in regulating kidney K^+ secretion in the distal nephron (17–19). First, aldosterone increases intracellular K^+ concentrations by stimulating the activity of the Na^+-K^+ ATPase in the basolateral membrane. Second, aldosterone stimulates Na^+ reabsorption across the luminal membrane, which increases the electronegativity of the lumen, thereby increasing the electrical gradient favoring K^+ secretion. Lastly, aldosterone has a direct effect on the luminal membrane to increase K^+ permeability (Figure 2).

Aldosterone is a steroid hormone that diffuses into cells of the distal nephron and binds to the mineralocorticoid receptor, a member of the nuclear hormone receptor family nuclear receptor subfamily 3 group C member 2. This interaction results in signal transduction affecting gene expression in the nucleus and transcription of proteins that stimulate reabsorption of Na^+ and excretion of K^+. Whereas the receptor has equal affinity for cortisol and aldosterone, the enzyme 11-β-hydroxysteroid dehydrogenase type 2 inactivates cortisol to inert cortisone, keeping the receptor free to interact only with aldosterone.

Effects of Aldosterone on K^+ Handling in Extrarenal Transporting Epithelia

In addition to its role in regulating salt and water transport in the kidney, aldosterone influences electrolyte transport in extrarenal tissues. In this regard, the mineralocorticoid receptor is found in numerous transporting epithelia, including the salivary gland, sweat gland, airway epithelia, and distal colon (Table 1). Administration of aldosterone to normal subjects lowers Na^+ and increases K^+ concentration in saliva (20). A similar but delayed effect also occurs in sweat (21). Disease states in which there is either a pathologic deficiency or excess of aldosterone alter Na^+ and K^+ concentration in saliva consistent with the changes reported in normal subjects given aldosterone. For example, the salivary Na^+/K^+ ratio is increased in patients

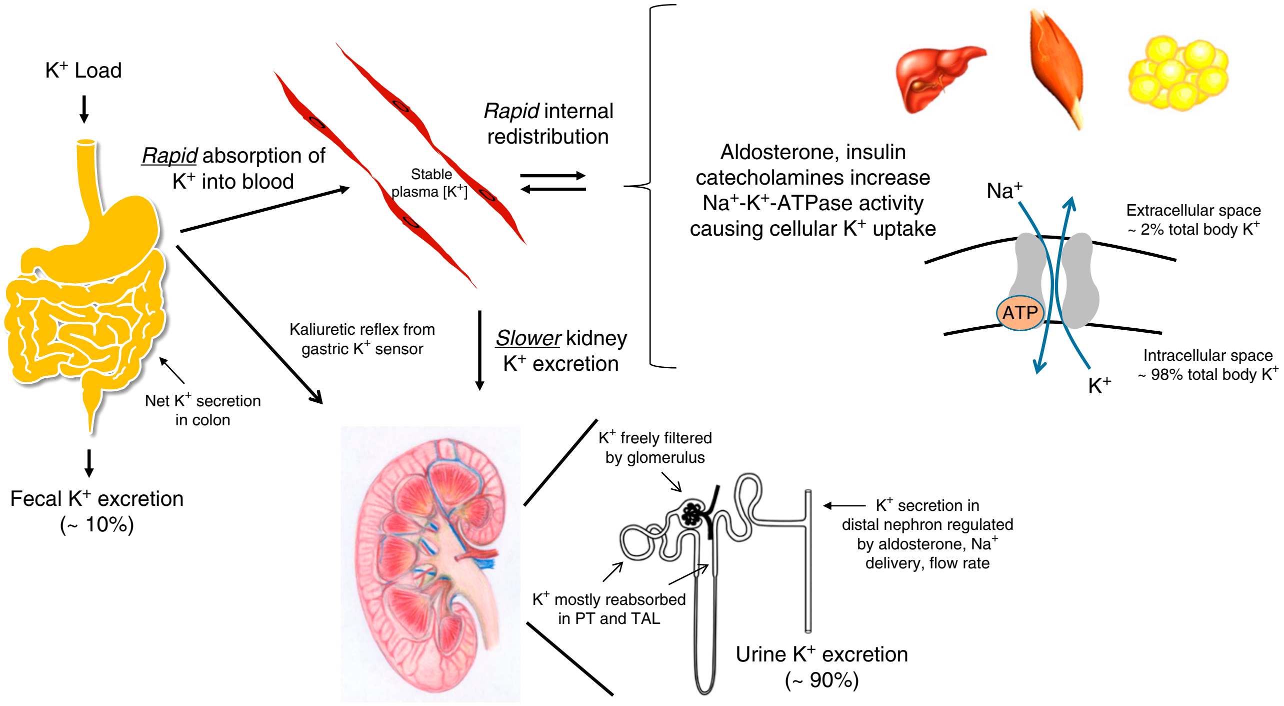

Figure 2. | **Overview of normal K$^+$ homeostasis.** Absorption of K$^+$ from the gastrointestinal tract is faster than kidney excretion, necessitating a shift of K$^+$ into the cell to guard against pathologic rises in extracellular K$^+$ concentration. Insulin, catecholamines, and aldosterone all act to shift K$^+$ into the intracellular space through effects that increase the activity of the Na$^+$-K$^+$-ATPase pump. Kidney K$^+$ excretion eventually matches dietary intake such that total body K$^+$ content is maintained within a narrow range. A brief summary of kidney K$^+$ handling is depicted. There is evidence that kidney K$^+$ excretion is initiated through a gastric-kidney signaling pathway as early as entry of dietary K$^+$ into the stomach. Approximately 10% of dietary K$^+$ is excreted in the colon. This component of K$^+$ handling increases as CKD progresses. PT, proximal tubule; TAL, thick ascending limb.

with Addison's disease, whereas the ratio is decreased in Cushing's disease (22,23). Low ratios are also found in patients with primary or secondary hyperaldosteronism. To be sure, in the absence of excessive sweating, changes in sweat or salivary gland K$^+$ transport are not of clinical relevance. Lastly, aldosterone augments Na$^+$ transport in airway epithelia by increasing the activity of the Na$^+$-K$^+$-ATPase pump (24).

Similar to the findings in sweat and saliva, aldosterone reduces Na$^+$ and increases K$^+$ secretion in the human colon. Under normal circumstances, the majority of dietary K$^+$ along with gastric, biliary, and pancreatic secretions is passively absorbed *via* solvent drag in the small intestine. The colon is a net secretor of K$^+$ through passive and active secretory mechanisms along with an active absorptive component (25). Passive K$^+$ secretion is paracellular and increases in magnitude along the length of the colon in parallel with the degree of luminal electronegativity, the latter of which is due to electrogenic Na$^+$ reabsorption. Mineralocorticoid-induced changes in Na$^+$ flux cause an increase in the transepithelial potential difference, which along with increased activity of the Na$^+$-K$^+$-ATPase pump result in increased K$^+$ secretion (26–29). In patients with primary and secondary hyperaldosteronism, the fecal Na$^+$/K$^+$ ratio is decreased. Aldosterone may also affect active K$^+$ secretion in the colon. This process consists of K$^+$ uptake *via* the Na$^+$-K$^+$-ATPase and the Na$^+$-K$^+$-Cl$^-$ cotransporter on the basolateral surface of the colonocyte and secretion through apical K$^+$ channels. Active K$^+$ absorption is mediated by an H$^+$-K$^+$-ATPase located on the apical membrane of the distal colon and is upregulated by dietary K$^+$ restriction. The increase in colonic K$^+$ secretion that accompanies loss of kidney function is primarily due to increased apical expression of large-conductance, Ca^{2+}-activated BK channels (30). This channel is upregulated by aldosterone and other mediators that elevate cAMP in the enterocyte, likely explaining why some patients on kidney replacement therapy develop hyperkalemia when prescribed renin-angiotensin-aldosterone blockers. An overview of how aldosterone regulates K$^+$ handling in the colon is provided in Figure 3.

Table 1. Tissues in which aldosterone exerts an effect on ion transport

- Distal nephron of the kidney
- Salivary gland
- Sweat gland
- Colon
- Airway epithelia

Effects of Aldosterone in Determining Internal K$^+$ Distribution

Although the extrarenal effects of aldosterone to modulate K$^+$ and Na$^+$ transport in salivary fluid, sweat, airway epithelia, and colonic fluid are well established, the role of aldosterone in determining the internal distribution of K$^+$ is less well defined and controversial. *In vitro* studies in

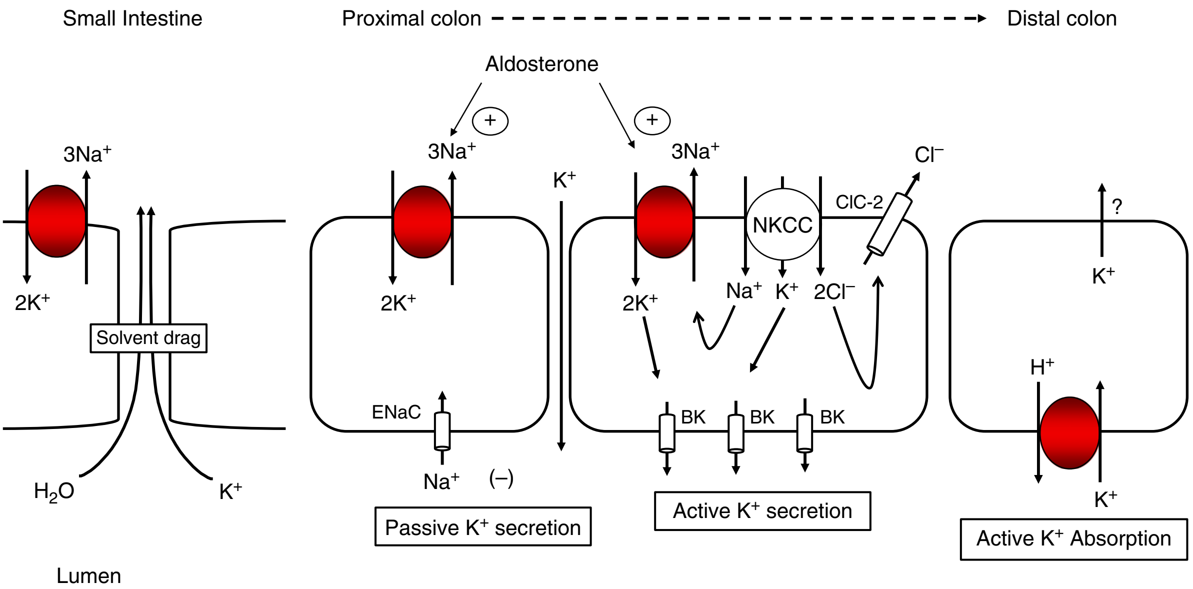

Figure 3. | **Influence of aldosterone on K^+ transport along the gastrointestinal tract.** K^+ absorption in the small bowel is primarily passive pulled by bulk water movement *via* solvent drag. K^+ secretion in the colon occurs by both a passive and active mechanism, both of which are stimulated by aldosterone. Aldosterone does not affect the small component of active K^+ absorption mediated by the apically located H^+-K^+-ATPase present in the terminal part of the colon. See text for discussion. Red indicates energy requiring transporter. BK, large-conductance, Ca^{2+}-activated K(Ca)1.1 (BK) channel; NKCC, Na^+-K^+-$2Cl^-$ cotransporter; ClC-2, chloride channel; ENaC, epithelial Na^+ channel.

which an isolated rat diaphragm is incubated with aldosterone demonstrate there are direct effects of the hormone on modulation of tissue K^+ content (31–33). *In vivo* studies are limited by the difficulty in accurately measuring overall K^+ balance and factoring in both variability and secondary changes in acid-base balance, systemic hemodynamics, and other K^+-regulatory factors such as hormones and adrenergic activity. Despite these limitations, the bulk of data suggest aldosterone does enhance extrarenal K^+ disposal.

Older studies examining K^+ balance in dogs found the increase in plasma K^+ after adrenalectomy is not accounted for by changes in gastrointestinal or kidney excretion (34,35). Similarly, changes in urine or stool K^+ do not explain the reduction in plasma K^+ when aldosterone is infused into normal rabbits (36,37). In rabbits subjected to nephrectomy, infusion of aldosterone maintains plasma K^+ concentration within normal limits and delays death form hyperkalemia. In a detailed examination of a patient with selective aldosterone deficiency and hyperkalemia, the plasma K^+ concentration decreased after administration of deoxycorticosterone acetate. This compound is an adrenally produced steroid hormone with potent mineralocorticoid activity but virtually devoid of glucocorticoid activity. Measurements in urine and stool showed no alteration in net K^+ excretion, suggesting the mineralocorticoid increased K^+ uptake into the intracellular compartment (38).

Rats fed a high-K^+ diet for several days are able to survive a subsequent acute load of K^+ that is otherwise lethal to animals fed a regular diet (39). In addition to enhanced urinary excretion, increases in tissue uptake mediated by aldosterone contribute to this adaptive response. In support, tolerance to the acute load is observed in the presence and absence of kidneys. In addition, adrenalectomy abolishes the tolerance to the acute load but is reproduced when repeated injections of mineralocorticoid are given over the course of several days before the acute K^+ load (38). Although these results support an important role for aldosterone in regulating the internal distribution of K^+, others have suggested the described experimental maneuvers may have caused the animals to become K^+ depleted before the acute challenge (40). According to this later interpretation, increased urinary K^+ excretion in response to several days of high intake may persist for a period of time (overshoot) after a sudden decrease in dietary K^+ predisposing to negative K^+ balance. Similarly, chronic administration of mineralocorticoid (particularly at high doses) may render the animals K^+ depleted. In the setting of total body depletion, the lack of increase in plasma K^+ after an acute load would represent replenishment of depleted intracellular stores as opposed to active shift into cells under the dictates of aldosterone.

Convincing evidence for the role of aldosterone to influence the distribution of K^+ between the intracellular and extracellular spaces comes from studies performed in adrenalectomized dogs given continuous intravenous replacement doses of aldosterone at varying rates along with incremental increases in dietary intake of K^+ maintained for 7–10 days (41,42). Total exchangeable K^+ and plasma K^+ were measured at the conclusion of each combination of aldosterone infusion rate and dietary K^+ intake period. As the rate of aldosterone infusion increased, the relationship between exchangeable K^+ and plasma K^+ was shifted downward. Stated differently, less K^+ resided in the extracellular space for a given total exchangeable K^+ as aldosterone levels increased.

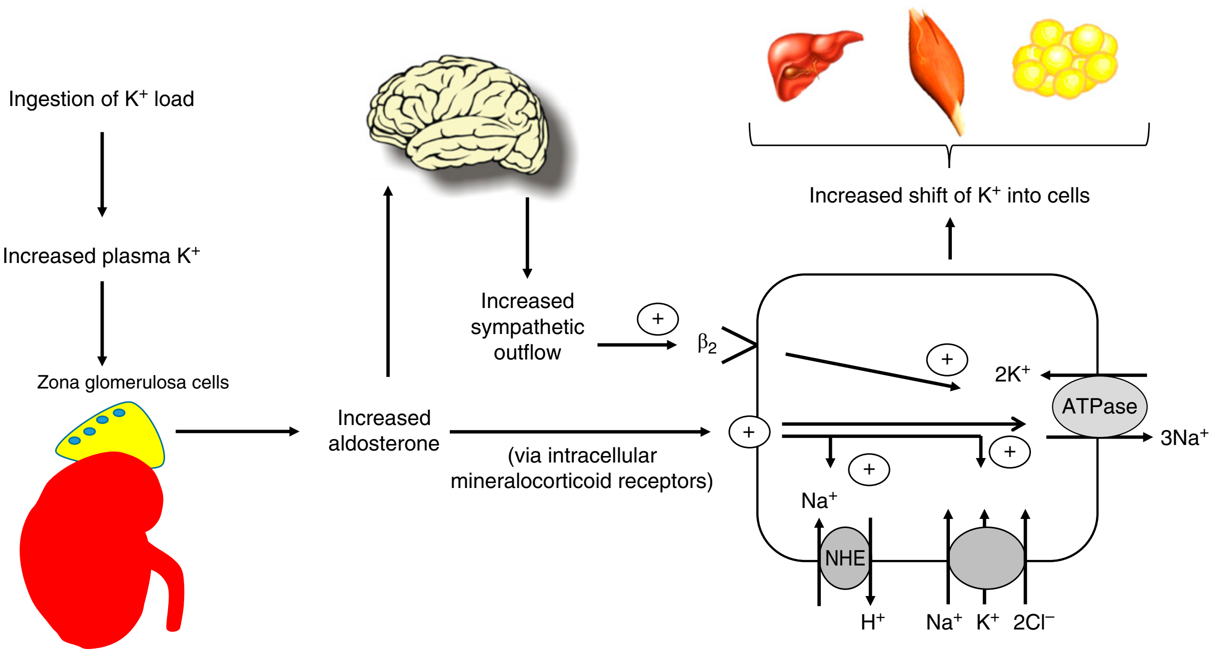

Figure 4. | Direct and indirect effects of aldosterone in mediating shift of K^+ into the intracellular space. Increases in plasma K^+ directly stimulates the release of aldosterone from the zona glomerulosa cells of the adrenal gland. Aldosterone binds to the mineralocorticoid receptor inside the cell and increases cell Na^+ concentration by increasing the activity of the Na^+-H^+ exchanger and the Na^+-K^+-$2Cl^-$ cotransporter. Increases in cell Na^+ concentration along with a direct effect of aldosterone leads to increase activity of the Na^+-K^+-ATPase pump causing K^+ uptake. Aldosterone binds to receptors in the central nervous system, causing increased sympathetic outflow, which further stimulates pump activity through β_2-adrenergic receptors. Not shown is that increased sympathetic activity can stimulate insulin release from the pancreas, providing an additional mechanism to augment cell K^+ uptake. A generic cell is provided to indicate identified transporters involved in K^+ uptake such as skeletal muscle myocytes, hepatocytes, adipocytes, and cardiac myocytes. Circled+sign, stimulatory effect.

Correction of hyperkalemia with mineralocorticoids in anuric patients on maintenance hemodialysis is consistent with either a shift of K^+ into cells or augmented intestinal secretion (43). In order to delineate better between these two possibilities, anephric dialysis patients were given an acute oral K^+ load after first being treated with either deoxycorticosterone 10-mg intramuscularly daily for 3 days or 100 mg spironolactone orally every 8 hours for the 3-day period (44). Prior administration of the mineralocorticoid decreased the rate of rise in plasma K^+ concentration after the acute challenge compared with the spironolactone-treated subjects. Importantly, stool Na^+ and K^+ concentrations were unaltered during the study. The effect on extrarenal homeostasis was most marked in the first 3 hours of the study but was no longer apparent between 3 and 13 hours. However, on the basis of volume of distribution measurements, K^+ continued to be translocated into the intracellular space during this later time frame. After the initial effects of aldosterone, dietary stimulation of insulin and/or increased catecholamine activity induced by eating may have mediated the ongoing extrarenal K^+ disposal.

Because insulin and catecholamines are important physiologic regulators of K^+ distribution within the body as previously discussed, it is not surprising these factors may also synergize with aldosterone to regulate cellular K^+ uptake. In glucocorticoid-replaced adrenalectomized rats infused with KCl after acute nephrectomy, the increment in plasma K^+ per amount of K^+ retained is significantly greater compared with controls (45). When the animals are acutely replaced with aldosterone before the challenge, the increment in K^+ is significantly less than in untreated animals but remains higher than in controls. Chronic administration of aldosterone leads to complete correction of the defect. In addition, the tolerance to the K^+ load is also totally corrected if the adrenalectomized rats are acutely replaced with epinephrine, suggesting deficiency of both aldosterone and epinephrine contribute to impaired K^+ tolerance in chronic adrenal insufficiency. The idea these two factors may work in concert comes from the observation that aldosterone binds to mineralocorticoid receptors in the brain, triggering an increase in sympathetic outflow (46,47) (Figure 4). This stimulatory effect is downregulated by estrogen, suggesting a sexually dimorphic interaction in the central nervous system (48).

In a separate study, glucocorticoid-replaced adrenalectomized rats developed a significantly greater rise in K^+ after an acute intravenous load (49). A similar defect developed in animals made insulinopenic by infusing somatostatin. In both instances, the inability to dispose of the K^+ load properly occurred, despite the urinary excretion of an identical percentage of the administered load. In a third group of animals with combined adrenal and insulin deficiency, the increment in plasma K^+ occurred earlier and remained elevated for a more prolonged period when compared with animals with insulinopenia or adrenalectomy alone. The greater degree of extrarenal K^+ intolerance in the combined group may have particular relevance to patients with diabetes mellitus, where hypoaldosteronism occurs with increased frequency. In addition, these patients are prone to autonomic neuropathy, potentially creating a situation where combined deficiencies in insulin, aldosterone, and catecholamines give rise to hyperkalemia due to defects in extrarenal homeostasis (50,51).

Tissue Heterogeneity in Aldosterone-Mediated K^+ Uptake

Most studies assume the primary effect of mineralocorticoids on internal K^+ distribution is mediated through effects on mineralocorticoid receptors in skeletal muscle (52,53). The precise mechanism by which aldosterone interacts with the receptor is not clear because 11-β-hydroxysteroid dehydrogenase type 2 has not been found in skeletal muscle, suggesting the receptor would likely be occupied by cortisol (54,55). On the other hand, there is a modest amount of the enzyme expressed in cardiac tissue (55,56). The presence of mineralocorticoid receptors in cardiac myocytes suggests aldosterone has a functional role in the heart (57). Aldosterone stimulates cellular uptake of Na^+ in cardiac myocytes, which in turn signals increased synthesis of Na^+-K^+-ATPase subunits (58). Increased pump density can contribute to sequestration of K^+ into the intracellular compartment of these cells. Aldosterone can also stimulate the pump through a nongenomic pathway. In addition to effects on the Na^+-H^+ exchanger, aldosterone stimulates Na^+ uptake in cardiac myocytes by activating the Na^+-K^+-$2Cl^-$ cotransporter (59). Increased Na^+ influx exerts an immediate effect to stimulate Na^+-K^+-ATPase pump activity.

Differing sensitivities to aldosterone might contribute to the contrasting response of skeletal muscle and the heart to conditions of total body K^+ depletion. By way of background, intracellular K^+ serves as a reservoir to limit the fall in extracellular K^+ concentrations occurring under pathologic conditions, leading to K^+ loss from the body. As an example, studies in military recruits undergoing training in a hot environment developed a 400 mmol reduction in total body K^+ over an 11-day period due to K^+ loss in sweat. Despite this deficit, the plasma K^+ concentration remained near normal limits (60).

Use of a K^+ clamp technique in rodents has provided insight as to how plasma K^+ is defended in states of total body depletion. Animals are infused with a constant amount of insulin and then administered parenteral K^+ at a rate to prevent drops in extracellular K^+ concentration. The amount of K^+ required to prevent hypokalemia reflects the amount of K^+ transported into the intracellular space of skeletal muscle (61). Insulin-mediated K^+ disappearance is reduced by >90% in animals subjected to 10 days of K^+ deprivation when compared with a control group. This decrease is accompanied by a >50% reduction in muscle Na^+-K^+-ATPase activity and expression. These data suggest skeletal muscle readily relinquishes intracellular stores of K^+ under conditions of K^+ loss from the body through decreased activity and number of ATPase pumps in an attempt to minimize the change in plasma K^+ concentration.

In contrast to the buffering effect of skeletal muscle, cardiac tissue K^+ content remains relatively well preserved in states of K^+ depletion (62,63). In addition, cardiac Na^+-K^+-ATPase pool size increases in K^+-deficient animals, unlike the decline in activity and expression in skeletal muscle. The increased in pool size in rats rendered K^+ depleted accounts for the greater clearance capacity after the administration of intravenous KCl when compared with K^+-replete controls. The cardiac capacity for K^+ uptake is comparable to that of skeletal muscle under conditions of K^+ depletion and may actually exceed skeletal muscle under control conditions when expressed on a weight basis. It is interesting to speculate and deserving of further study whether differences in sensitivity to aldosterone might contribute to the contrasting effects in K^+ distribution between skeletal muscle and the heart.

Discussion

Although the role of aldosterone in regulating kidney K^+ excretion is well established, there has been controversy as to the role played by aldosterone in dictating the distribution of K^+ across the cell membrane. When viewed from the context that mineralocorticoid receptors are widely distributed to include skeletal muscle and the myocardium, the bulk of data support at least a contributory role of aldosterone in internal K^+ homeostasis. The ability of aldosterone to act centrally to stimulate sympathetic activity, which in turn stimulates insulin release, suggests these three factors may work in concert to influence K^+ distribution within the body. Still unexplored are differences in tissue sensitivity to the effects of aldosterone and what role these differences may play under condition of totally body K^+ depletion.

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Author Contributions

Both authors wrote the original draft, reviewed, and edited the manuscript.

References

1. Palmer BF: Potassium binders for hyperkalemia in chronic kidney disease-diet, renin-angiotensin-aldosterone system inhibitor therapy, and hemodialysis. *Mayo Clin Proc* 95: 339–354, 2020 https://doi.org/10.1016/j.mayocp.2019.05.019
2. Bia MJ, DeFronzo RA: Extrarenal potassium homeostasis. *Am J Physiol* 240: F257–F268, 1981
3. Brown RS: Extrarenal potassium homeostasis. *Kidney Int* 30: 116–127, 1986 https://doi.org/10.1038/ki.1986.160
4. Ho K: A critically swift response: Insulin-stimulated potassium and glucose transport in skeletal muscle. *Clin J Am Soc Nephrol* 6: 1513–1516, 2011 https://doi.org/10.2215/CJN.04540511
5. Therien AG, Blostein R: Mechanisms of sodium pump regulation. *Am J Physiol Cell Physiol* 279: C541–C566, 2000 https://doi.org/10.1152/ajpcell.2000.279.3.C541
6. Nguyen TQ, Maalouf NM, Sakhaee K, Moe OW: Comparison of insulin action on glucose versus potassium uptake in humans. *Clin J Am Soc Nephrol* 6: 1533–1539, 2011 https://doi.org/10.2215/CJN.00750111

7. Santeusanio F, Faloona GR, Knochel JP, Unger RH: Evidence for a role of endogenous insulin and glucagon in the regulation of potassium homeostasis. *J Lab Clin Med* 81: 809–817, 1973
8. Hiatt N, Yamakawa T, Davidson MB: Necessity for insulin in transfer of excess infused K to intracellular fluid. *Metabolism* 23: 43–49, 1974 https://doi.org/10.1016/0026-0495(74)90102-4
9. DeFronzo RA, Sherwin RS, Dillingham M, Hendler R, Tamborlane WV, Felig P: Influence of basal insulin and glucagon secretion on potassium and sodium metabolism. Studies with somatostatin in normal dogs and in normal and diabetic human beings. *J Clin Invest* 61: 472–479, 1978 https://doi.org/10.1172/JCI108958
10. Perry MC, Hales CN: Rates of efflux and intracellular concentrations of potassium, sodium and chloride ions in isolated fat-cells from the rat. *Biochem J* 115: 865–871, 1969 https://doi.org/10.1042/bj1150865
11. Williams ME, Gervino EV, Rosa RM, Landsberg L, Young JB, Silva P, Epstein FH: Catecholamine modulation of rapid potassium shifts during exercise. *N Engl J Med* 312: 823–827, 1985 https://doi.org/10.1056/NEJM198503283121304
12. Clifford PS: Skeletal muscle vasodilatation at the onset of exercise. *J Physiol* 583: 825–833, 2007 https://doi.org/10.1113/jphysiol.2007.135673
13. Clausen T, Nielsen OB: Potassium, Na+,K+-pumps and fatigue in rat muscle. *J Physiol* 584: 295–304, 2007 https://doi.org/10.1113/jphysiol.2007.136044
14. McKenna, MJ, Bangsbo, J, Renaud, JM: Muscle K+, Na+, and Cl disturbances and Na+-K+ pump inactivation: Implications for fatigue. *J Appl Physiol (1985)* 104: 288–295, 2008 https://doi.org/0.1152/japplphysiol.01037.2007
15. Ewart HS, Klip A: Hormonal regulation of the Na(+)-K(+)-ATPase: Mechanisms underlying rapid and sustained changes in pump activity. *Am J Physiol* 269: C295–C311, 1995 https://doi.org/10.1152/ajpcell.1995.269.2.C295
16. Allon M, Shanklin N: Adrenergic modulation of extrarenal potassium disposal in men with end-stage renal disease. *Kidney Int* 40: 1103–1109, 1991 https://doi.org/10.1038/ki.1991.321
17. Palmer BF, Clegg DJ: Physiology and pathophysiology of potassium homeostasis: Core curriculum 2019. *Am J Kidney Dis* 74: 682–695, 2019 https://doi.org/10.1053/j.ajkd.2019.03.427
18. Palmer BF: Regulation of potassium homeostasis. *Clin J Am Soc Nephrol* 10: 1050–1060, 2015 https://doi.org/10.2215/CJN.08580813
19. Palmer BF, Clegg DJ: Physiology and pathophysiology of potassium homeostasis. *Adv Physiol Educ* 40: 480–490, 2016 https://doi.org/10.1152/advan.00121.2016
20. Adlin V, Channick BJ, Marks AD: Salivary sodium-potassium ratio and plasma renin activity in hypertension. *Circulation* 39: 685–692, 1969 https://doi.org/10.1161/01.CIR.39.5.685
21. Emrich HM, Stoll E, Rossi E: [Aldosterone effect on the sodium chloride and potassium excretion in the sweat of cystic fibrosis patients and healthy persons]. *Klin Wochenschr* 48: 966–972, 1970 https://doi.org/10.1007/BF01484399
22. Thorn GW, Forsham PH, Frawley TF, Wilson DL, Renold AE, Fredrickson DS, Jenkins D: Advances in the diagnosis and treatment of adrenal insufficiency. *Am J Med* 10: 595–611, 1951 https://doi.org/10.1016/0002-9343(51)90330-0
23. Catalanotto FA, Sweeney EA: Salivary sodium and potassium concentrations in adrenalectomized rats. *Behav Biol* 24: 467–473, 1978 https://doi.org/10.1016/S0091-6773(78)90803-9
24. Olivera WG, Ciccolella DE, Barquin N, Ridge KM, Rutschman DH, Yeates DB, Sznajder JI: Aldosterone regulates Na,K-ATPase and increases lung edema clearance in rats. *Am J Respir Crit Care Med* 161: 567–573, 2000 https://doi.org/10.1164/ajrccm.161.2.9808050
25. Rajendran VM, Sandle GI: Colonic potassium absorption and secretion in health and disease. *Compr Physiol* 8: 1513–1536, 2018 https://doi.org/10.1002/cphy.c170030
26. Charron RC, Leme CE, Wilson DR, Ing TS, Wrong OM: The effect of adrenal steroids on stool composition, as revealed by *in vivo* dialysis of faeces. *Clin Sci* 37: 151–167, 1969
27. Richards P: Clinical investigation of the effects of adrenal corticosteroid excess on the colon. *Lancet* 1: 437–442, 1969 https://doi.org/10.1016/S0140-6736(69)91480-9
28. Edmonds CJ, Marriott JC: The effect of aldosterone on the electrical activity of rat colon. *J Endocrinol* 44: 363–377, 1969 https://doi.org/10.1677/joe.0.0440363
29. Thompson BD, Edmonds CJ: Comparison of effects of prolonged aldosterone administration on rat colon and renal electrolyte excretion. *J Endocrinol* 50: 163–169, 1971 https://doi.org/10.1677/joe.0.0500163
30. Sausbier M, Matos JE, Sausbier U, Beranek G, Arntz C, Neuhuber W, Ruth P, Leipziger J: Distal colonic K(+) secretion occurs *via* BK channels. *J Am Soc Nephrol* 17: 1275–1282, 2006 https://doi.org/10.1681/ASN.2005101111
31. Fluckiger E, Verzar F: [Effect of aldosterone on sodium, potassium and glycogen metabolism in isolated muscle]. *Experientia* 10: 259–261, 1954
32. Adler S: An extrarenal action of aldosterone on mammalian skeletal muscle. *Am J Physiol* 218: 616–621, 1970 https://doi.org/10.1152/ajplegacy.1970.218.3.616
33. Lim VS, Webster GD: The effect of aldosterone on water and electrolyte composition of incubated rat diaphragms. *Clin Sci* 33: 261–270, 1967
34. Loeb RF, Atchley DW, Benedict EM, Leland J: Electrolyte balance studies in adrenalectomized dogs with particular references to the excretion of sodium. *J Exp Med* 57: 775–792, 1933 https://doi.org/10.1084/jem.57.5.775
35. Stern TN, Cole VV, Bass AC, Overman RR: Dynamic aspects of sodium metabolism in experimental adrenal insufficiency using radioactive sodium. *Am J Physiol* 164: 437–449, 1951 https://doi.org/10.1152/ajplegacy.1951.164.2.437
36. Dawborn JK, Ross EJ: The effect of prolonged administration of aldosterone on sodium and potassium turnover in the rabbit. *Clin Sci* 32: 559–570, 1967
37. Dawborn JK, Watson L: Effect of prolonged administration of aldosterone on potassium and magnesium metabolism in the rabbit. *Med J Aust* 2: 304–307, 1968 https://doi.org/10.5694/j.1326-5377.1968.tb82781.x
38. DeFronzo RA: Hyperkalemia and hyporeninemic hypoaldosteronism. *Kidney Int* 17: 118–134, 1980 https://doi.org/10.1038/ki.1980.14
39. Alexander EA, Levinsky NG: An extrarenal mechanism of potassium adaptation. *J Clin Invest* 47: 740–748, 1968 https://doi.org/10.1172/JCI105769
40. Spital A, Sterns RH: Paradoxical potassium depletion: A renal mechanism for extrarenal potassium adaptation. *Kidney Int* 30: 532–537, 1986 https://doi.org/10.1038/ki.1986.218
41. Young DB: Quantitative analysis of aldosterone's role in potassium regulation. *Am J Physiol* 255: F811–F822, 1988 https://doi.org/10.1152/ajprenal.1988.255.5.F811
42. Young DB, Jackson TE: Effects of aldosterone on potassium distribution. *Am J Physiol* 243: R526–R530, 1982
43. Furuya R, Kumagai H, Sakao T, Maruyama Y, Hishida A: Potassium-lowering effect of mineralocorticoid therapy in patients undergoing hemodialysis. *Nephron* 92: 576–581, 2002 https://doi.org/10.1159/000064116
44. Sugarman A, Brown RS: The role of aldosterone in potassium tolerance: Studies in anephric humans. *Kidney Int* 34: 397–403, 1988 https://doi.org/10.1038/ki.1988.194
45. Bia MJ, Tyler KA, DeFronzo RA: Regulation of extrarenal potassium homeostasis by adrenal hormones in rats. *Am J Physiol* 242: F641–F644, 1982 https://doi.org/10.1152/ajprenal.1982.242.6.F641
46. Takahashi H, Yoshika M, Komiyama Y, Nishimura M: The central mechanism underlying hypertension: A review of the roles of sodium ions, epithelial sodium channels, the renin-angiotensin-aldosterone system, oxidative stress and endogenous digitalis in the brain. *Hypertens Res* 34: 1147–1160, 2011 https://doi.org/10.1038/hr.2011.105
47. Xue B, Beltz TG, Yu Y, Guo F, Gomez-Sanchez CE, Hay M, Johnson AK: Central interactions of aldosterone and angiotensin II in aldosterone- and angiotensin II-induced hypertension. *Am J Physiol Heart Circ Physiol* 300: H555–H564, 2011 https://doi.org/10.1152/ajpheart.00847.2010

48. Xue B, Johnson AK, Hay M: Sex differences in angiotensin II- and aldosterone-induced hypertension: The central protective effects of estrogen. *Am J Physiol Regul Integr Comp Physiol* 305: R459–R463, 2013 https://doi.org/10.1152/ajpregu.00222.2013
49. DeFronzo RA, Lee R, Jones A, Bia M: Effect of insulinopenia and adrenal hormone deficiency on acute potassium tolerance. *Kidney Int* 17: 586–594, 1980 https://doi.org/10.1038/ki.1980.69
50. Palmer BF, Clegg DJ: Electrolyte and acid-base disorders in patients with diabetes mellitus. *N Engl J Med* 373: 548–559, 2015 https://doi.org/10.1056/NEJMra1503102
51. Perez GO, Lespier L, Knowles R, Oster JR, Vaamonde CA: Potassium homeostasis in chronic diabetes mellitus. *Arch Intern Med* 137: 1018–1022, 1977 https://doi.org/10.1001/archinte.1977.03630200026010
52. Chadwick JA, Hauck JS, Lowe J, Shaw JJ, Guttridge DC, Gomez-Sanchez CE, Gomez-Sanchez EP, Rafael-Fortney JA: Mineralocorticoid receptors are present in skeletal muscle and represent a potential therapeutic target. *FASEB J* 29: 4544–4554, 2015 https://doi.org/10.1096/fj.15-276782
53. Phakdeekitcharoen B, Kittikanokrat W, Kijkunasathian C, Chatsudthipong V: Aldosterone increases Na+-K+-ATPase activity in skeletal muscle of patients with Conn's syndrome. *Clin Endocrinol (Oxf)* 74: 152–159, 2011 https://doi.org/10.1111/j.1365-2265.2010.03912.x
54. Gomez-Sanchez EP, Gomez-Sanchez CE: 11β-hydroxysteroid dehydrogenases: A growing multi-tasking family. *Mol Cell Endocrinol* 526: 111210, 2021 https://doi.org/10.1016/j.mce.2021.111210
55. Náray-Fejes-Tóth A, Fejes-Tóth G: Novel mouse strain with Cre recombinase in 11β-hydroxysteroid dehydrogenase-2-expressing cells. *Am J Physiol Renal Physiol* 292: F486–F494, 2007 https://doi.org/10.1152/ajprenal.00188.2006
56. Bauersachs J, Jaisser F, Toto R: Mineralocorticoid receptor activation and mineralocorticoid receptor antagonist treatment in cardiac and renal diseases. *Hypertension* 65: 257–263, 2015 https://doi.org/10.1161/HYPERTENSIONAHA.114.04488
57. Hawkins UA, Gomez-Sanchez EP, Gomez-Sanchez CM, Gomez-Sanchez CE: The ubiquitous mineralocorticoid receptor: Clinical implications. *Curr Hypertens Rep* 14: 573–580, 2012 https://doi.org/10.1007/s11906-012-0297-0
58. Ikeda U, Hyman R, Smith TW, Medford RM: Aldosterone-mediated regulation of Na+, K(+)-ATPase gene expression in adult and neonatal rat cardiocytes. *J Biol Chem* 266: 12058–12066, 1991 https://doi.org/10.1016/S0021-9258(18)99065-4
59. Mihailidou AS, Buhagiar KA, Rasmussen HH: Na+ influx and Na(+)-K+ pump activation during short-term exposure of cardiac myocytes to aldosterone. *Am J Physiol* 274: C175–C181, 1998 https://doi.org/10.1152/ajpcell.1998.274.1.C175
60. Knochel JP, Dotin LN, Hamburger RJ: Pathophysiology of intense physical conditioning in a hot climate. I. Mechanisms of potassium depletion. *J Clin Invest* 51: 242–255, 1972 https://doi.org/10.1172/JCI106809
61. McDonough AA, Youn JH: Role of muscle in regulating extracellular [K+]. *Semin Nephrol* 25: 335–342, 2005 https://doi.org/10.1016/j.semnephrol.2005.03.009
62. Bundgaard H, Kjeldsen K: Potassium depletion increases potassium clearance capacity in skeletal muscles *in vivo* during acute repletion. *Am J Physiol Cell Physiol* 283: C1163–C1170, 2002 https://doi.org/10.1152/ajpcell.00588.2001
63. Bundgaard H: Potassium depletion improves myocardial potassium uptake *in vivo*. *Am J Physiol Cell Physiol* 287: C135–C141, 2004 https://doi.org/10.1152/ajpcell.00580.2003

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