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Key Points:

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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 non-transporting 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.
I. Introduction

The plasma potassium (K\textsuperscript{+}) concentration is maintained within a narrow range following ingestion of a K\textsuperscript{+} load. This near constancy of plasma K\textsuperscript{+} is somewhat surprising since K\textsuperscript{+} is quickly absorbed by the gastrointestinal tract but the kidney excretes only one-half of the load during the first 4-6 hours following 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\textsuperscript{+} into the cell to allow enough time for the kidney to reestablish total body K\textsuperscript{+} content. Were it not for these factors, ingestion of a typical meal could potentially double the extracellular K\textsuperscript{+} concentration producing life threatening hyperkalemia since only 2% of total body K\textsuperscript{+} (55-65 mEq) is found in the extracellular compartment. The degree to which plasma K\textsuperscript{+} increases following a meal is dependent on the makeup of the diet, the magnitude of decreased kidney function, and 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\textsuperscript{+} across the cell. The role of insulin and catecholamines in regulating the internal distribution of K\textsuperscript{+} will be briefly discussed since these two factors play an important role in day to day physiology of K\textsuperscript{+} homeostasis. A more extensive review of the literature will focus on the role played by aldosterone in maintaining the internal distribution of K\textsuperscript{+}. The role of pathologic conditions that alter K\textsuperscript{+} distribution across the cell such as acid base disorder and changes in tonicity have been reviewed elsewhere and therefore will not be addressed (2,3).

II. 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 as well as increased cell Na\(^+\) concentration resulting from stimulation of Na\(^+\)/H\(^+\) exchanger (5) (Figure 1). In patients with the metabolic syndrome, insulin resistance, or chronic kidney disease, insulin-mediated glucose uptake is impaired but cellular K\(^+\) uptake remains normal demonstrative of divergent intracellular pathways regulating insulin mediated glucose and K\(^+\) uptake following 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 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.

III. 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 to 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). While 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 β₂ adrenergic receptors limit the rise in extracellular K⁺ concentration during exercise. β₂ 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. Following cessation of exercise, α-stimulation promotes K⁺ exit from the cell minimizing development of hypokalemia due to persistent β₂ receptor stimulation from residual circulating catecholamines. These effects explain observations that propranolol exacerbates and prolongs the increase in K⁺ during exercise while α-blockade with phentolamine lowers the K⁺ level during recovery. Increased afferent nerve activity originating in the diseased kidney of patients with end-stage kidney disease contributes to increased sympathetic outflow and can exacerbate exercise and fasting-related hyperkalemia due to α-adrenergic receptor stimulation (16).
IV. 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 NR3C2 (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⁺. While 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.

A. Effects of Aldosterone on K⁺ Handling in Extra-Renal 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 to include 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 alters 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 with Addison’s disease while the ratio is decreased in Cushing’s disease (22,23). Low ratios are also been 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.

B. Effects of Aldosterone in Determining Internal K\(^+\) Distribution

While the extrarenal effects of aldosterone to modulate K\(^+\) and Na\(^+\) transport in salivary fluid, sweat, airway epithelia, and colonic fluid is well established, the role of aldosterone in determining the internal distribution of K\(^+\) is less well defined and controversial. In vitro studies in 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\(^+\) following 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 from hyperkalemia. In a detailed examination of a patient with selective aldosterone deficiency and hyperkalemia, the plasma K\(^+\) concentration decreased following 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 prior to the acute $K^+$ load (38). While 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 prior to 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) following 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 $K^+$ following 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
Total exchangeable $\text{K}^+$ and plasma $\text{K}^+$ were measured at the conclusion of each combination of aldosterone infusion rate and dietary $\text{K}^+$ intake period. As the rate of aldosterone infusion increased, the relationship between exchangeable $\text{K}^+$ and plasma $\text{K}^+$ was shifted downward. Stated differently, less $\text{K}^+$ resided in the extracellular space for a given total exchangeable $\text{K}^+$ as aldosterone levels increased.

Correction of hyperkalemia with mineralocorticoids in anuric patients on maintenance hemodialysis is consistent with either/or a shift of $\text{K}^+$ into cells or augmented intestinal secretion (43). In order to better delineate between these 2 possibilities, anephric dialysis patients were given an acute oral $\text{K}^+$ load after being first treated with either deoxycorticosterone 10 mg intramuscularly daily for three days or 100 mg spironolactone orally every eight hours for the three day period (44). Prior administration of the mineralocorticoid decreased the rate of rise in plasma $\text{K}^+$ concentration following the acute challenge when compared to the spironolactone treated subjects. Importantly, stool $\text{Na}^+$ and $\text{K}^+$ 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, based on volume of distribution measurements, $\text{K}^+$ 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 $\text{K}^+$ disposal.

Since insulin and catecholamines are important physiologic regulators of $\text{K}^+$ distribution within the body as previously discussed, it is not surprising these factors may also synergize with aldosterone to regulate cellular $\text{K}^+$ uptake. In glucocorticoid replaced adrenalectomized rats infused with KCl after acute nephrectomy, the increment in plasma $\text{K}^+$ per amount of $\text{K}^+$ retained is significantly greater as compared to controls (45). When the animals are acutely replaced with
aldosterone prior to 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\(^+\) following an acute intravenous load (49). A similar defect developed in animals made insulinopenic by infusing somatostatin. In both instances, the inability to properly dispose of the K\(^+\) load 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 to 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).

V. 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 since 11-$\beta$-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 suggest 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 $Na^+\cdot K^+\cdot$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 non-genomic pathway. In addition to effects on the $Na^+\cdot H^+$ exchanger, aldosterone stimulates $Na^+$ uptake in cardiac myocytes by activating the $Na^+\cdot K^+\cdot 2Cl^-$ cotransporter (59). Increased $Na^+$ influx exerts an immediate effect to stimulate $Na^+\cdot K^+\cdot$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 to a control group. This decrease is accompanied by a greater than 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 following the administration of intravenous KCl when compared to 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.

Summary

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

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

Figure 1. **Cell model illustrating β<sub>2</sub>-adrenergic and insulin mediated regulatory pathways for K<sup>+</sup> uptake in skeletal muscle.** β<sub>2</sub>-adrenergic stimulation and insulin both lead to K<sup>+</sup> uptake by stimulating the activity of the Na<sup>+</sup>-K<sup>+</sup>-ATPase pump primarily in skeletal muscle but do so through different signaling pathways. β<sub>2</sub>-adrenergic stimulation leads to increase pump activity through a cAMP (cyclic AMP or 3'-5'-cyclic adenosine monophosphate) and PKA (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 PI3-K (phosphatidylinositide 3-kinase). The IRS-1-PI3-K interaction leads to activation of PDK1 (3-phosphoinositide dependent protein kinase-1). The stimulatory effect of insulin on glucose uptake and K<sup>+</sup> uptake diverge at this point. An Akt (serine/threonine protein kinase) dependent pathway is responsible for membrane insertion of the glucose transporter type 4 (GLUT4), whereas activation of aPKC (atypical protein kinase C) leads to membrane insertion of the Na<sup>+</sup>-K<sup>+</sup>-ATPase pump. Not shown is that insulin stimulates pump activity by increasing cell Na<sup>+</sup> brought about by a stimulatory effect on the Na<sup>+</sup>-H<sup>+</sup> antiporter.

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

Figure 3. **Influence of aldosterone on K<sup>+</sup> transport along the gastrointestinal tract.** K<sup>+</sup> absorption in the small bowel is primarily passive pulled by bulk water movement via solvent drag. K<sup>+</sup> 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 color 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

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 \(\beta_2\)-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
K\textsuperscript{+} Load

\underline{Rapid} absorption of K\textsuperscript{+} into blood

\underline{Rapid} internal redistribution

Stable plasma [K\textsuperscript{+}]

\underline{Slower} kidney K\textsuperscript{+} excretion

Net K\textsuperscript{+} secretion in colon

Fecal K\textsuperscript{+} excretion (~ 10%)

Aldosterone, insulin catecholamines increase Na\textsuperscript{+}-K\textsuperscript{+}-ATPase activity causing cellular K\textsuperscript{+} uptake

\underline{K\textsuperscript{+} freely filtered by glomerulus}

\underline{K\textsuperscript{+} mostly reabsorbed in PT and TAL}

\underline{K\textsuperscript{+} secretion in distal nephron regulated by aldosterone, Na\textsuperscript{+} delivery, flow rate}

\underline{Urine K\textsuperscript{+} excretion (~ 90%)}

\underline{Extracellular space ~ 2% total body K\textsuperscript{+}}

\underline{Intracellular space ~ 98% total body K\textsuperscript{+}}

Fig 2
Figure 3

Small Intestine

Proximal colon

Distal colon

Aldosterone

3Na\(^+\)

2K\(^+\)

3Na\(^+\)

K\(^+\)

3Na\(^+\)

K\(^+\)

2K\(^+\)

2K\(^+\)

2K\(^+\)

Na\(^+\)

Na\(^+\)

H\(_2\)O

K\(^+\)

ENaC

Passive K\(^+\) secretion

Active K\(^+\) secretion

Active K\(^+\) Absorption

H\(^+\)

K\(^+\)

Lumen

Fig 3
Ingestion of $K^+$ load

$\rightarrow$

Increased plasma $K^+$

$\rightarrow$

Zona glomerulosa cells

Increased aldosterone

$\rightarrow$

Increased sympathetic outflow

$\rightarrow$

Increased shift of $K^+$ into cells

Figure 4

(via intracellular mineralocorticoid receptors)

$\beta_2$

$\rightarrow$

$2K^+$

$3Na^+$

$\rightarrow$

$\rightarrow$

$\rightarrow$

$\rightarrow$

$\rightarrow$

$\rightarrow$