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REVIEW

The Unappreciated Role of Extrarenal and Gut Sensors in Modulating Renal Potassium Handling: Implications for Diagnosis of Dyskalemias and Interpreting Clinical Trials

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In addition to the classic and well-established "feedback control" of potassium balance, increasing investigative attention has focused on a novel and not widely recognized complementary regulatory paradigm for maintaining potassium homeostasis—the "feed-forward control" of potassium balance. This regulatory mechanism, initially defined in rumen, has recently been validated in normal human subjects. Studies are being conducted to determine the location for this putative potassium sensor and to evaluate potential signals, which might increase renal potassium excretion. Awareness of this more updated integrative control mechanism for potassium homeostasis is ever more relevant today, when the medical community is increasingly focused on the challenges of managing the hyperkalemia provoked by renin–angiotensin–aldosterone system inhibitors (RAASis). Recent studies have demonstrated a wide gap between RAASi prescribing guidelines and real-world experience and have highlighted that this gap is thought to be attributable in great part to hyperkalemia. Consequently we require a greater knowledge of the complexities of the regulatory mechanisms subserving potassium homeostasis. Sodium polystyrene sulfonate has long been the mainstay for treating hyperkalemia, but its administration is fraught with challenges related to patient discomfort and colonic necrosis. The current and imminent availability of newer potassium binders with better tolerability and more predictive dose–response potassium removal should enhance the management of hyperkalemia. Consequently it is essential to better understand the intricacies of mammalian colonic K^+ handling. We discuss colonic transport of K^+ and review evidence for potassium (BK) channels being responsible for increased stool K^+ in patients with diseases such as ulcerative colitis.

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The integrated mechanisms controlling the maintenance of potassium homeostasis are well established and are defined by the classic "feedback control" of potassium balance. In recent years, increasing investigative attention has focused on novel physiological paradigms that increase the complexity but also the precision of homeostasis. In this Review we will briefly consider the classic and well-established "feedback control" of potassium and then consider subsequent investigations that inform on an intriguing and not widely recognized complementary paradigm—the "feed-forward" control of potassium balance. Awareness of this more updated integrative control mechanism for potassium homeostasis is ever more relevant today at a time when the medical community is increasingly focused on the challenges of managing the hyperkalemia provoked by renin–angiotensin–aldosterone system inhibitors (RAASis).[1–11]

It is well established that RAASis confer substantive benefits, such as reducing cardiovascular events and retarding progression of renal disease in several disease states, including congestive heart failure, chronic kidney disease, and diabetes.[12–23] Regretfully, treatment with RAASis can be complicated by hyperkalemia, which is a frequent side effect of RAASi therapy.[1–4,9–11] Indeed, the problem will only become increasingly prominent and frequent, because hyperkalemia will remain an issue with newly introduced drugs such as neprolysin

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inhibitors (LCZ-696)—as reported in the PARADIGM Heart Failure Study.[24] Furthermore, the wide gap between RAASi prescribing guidelines and reality is widely thought to be attributable to hyperkalemia.[1–4,9–11] As a consequence, we require a greater knowledge of the complexities of the regulatory mechanisms subserving potassium homeostasis. Finally, with the imminent availability of newer polymer resins to control hyperkalemia,[2,4–7,9] it is essential to understand how these newer drug agents may interact with the new resin binders. We require effective and safe treatments to control hyperkalemia, which in turn will facilitate treatment with optimal recommended doses of RAASis. Such a treatment paradigm should preclude unwanted down-titration and discontinuation of these life-saving medications, which have recently been documented to positively impact cardiorenal outcomes.[3,9–11]

Normal Potassium Balance and Renal Potassium Excretion

In order to establish the context and foundation for considering newer, albeit poorly recognized adaptive mechanisms for subserving potassium homeostasis, we will first summarize key concepts of steady-state potassium handling. Normal persons who consume a typical Western diet ingest approximately 70 to 80 mmol of potassium per day.[25,26] The intestine absorbs virtually all of the ingested potassium and delivers it to the liver for processing by means of the hepatoportal circulation. In normal circumstances, minimal amounts of potassium are excreted in the feces.

The principal defense against chronic potassium imbalances is renal potassium excretion, which depends on free filtration at the glomerulus, extensive proximal tubule reabsorption, and a highly regulated secretory process in the distal convoluted tubule and segments of the collecting duct in the cortex and outer medulla (the cortical collecting duct and the outer medullary collecting duct, respectively). Principal cells, which constitute approximately 75% of collecting duct cells, mediate sodium reabsorption and potassium secretion and also constitute targets for angiotensin II,[27] aldosterone, mineralocorticoid receptor antagonists, and potassium-sparing diuretics (Figure 1).

K^+ Transport in the Proximal Tubule

K^+ reabsorption in the proximal tubule primarily occurs through the paracellular pathway. Active Na^+ reabsorption drives net fluid reabsorption across the proximal tubule, which, in turn, promotes K^+ reabsorption by a solvent drag mechanism. As fluid flows down the proximal tubule, the luminal voltage shifts from slightly negative to slightly positive. The shift in transepithelial voltage provides an additional driving force favoring K^+ diffusion through the low-resistance paracellular pathway. K^+ uptake through the Na^+-K^+-ATPase pump can exit the basolateral membrane through a conductive pathway or coupled to Cl^-. An apically located K^+ channel functions to stabilize the cell negative potential, particularly in the setting of Na^+-coupled cotransport of glucose and amino acids, which has a depolarizing effect on cell voltage.

K^+ Transport in the Thick Ascending Limb of Henle

K^+ reabsorption occurs by both paracellular and transcellular mechanisms. The basolateral Na^+-K^+-ATPase pump maintains intracellular Na^+ low, thereby producing a favorable gradient to drive the apically located Na^+-K^+-$2Cl^-$ cotransporter (an example of secondary active transport). The apically located renal outer medullary K^+ (ROMK) channel provides a pathway for K^+ to recycle from cell to lumen, and ensures an adequate supply of K^+ to sustain Na^+-K^+-$2Cl^-$ cotransport. This movement through ROMK creates a lumen-positive voltage, providing a driving force for passive K^+ reabsorption through the paracellular pathway. Some of the K^+ entering the cell through the cotransporter exits the cell across the basolateral membrane, accounting for transcellular K^+ reabsorption. K^+ can exit the cell through a conductive pathway or in cotransport with Cl^-. ClC-Kb is the primary pathway for Cl^- efflux across the basolateral membrane.

K^+ Transport in the Distal Convoluted Tubule

In the early distal convoluted tubule (DCT), luminal Na^+ uptake is mediated by the apically located thiazide-sensitive Na^+-Cl^- cotransporter. This transporter is energized by the basolateral Na^+-K^+-ATPase, which maintains intracellular Na^+ concentration low, thereby providing a favorable gradient for Na^+ entry into the cell through secondary active transport. Whereas the cotransporter is abundantly expressed in the DCT1, it declines progressively along the DCT2.

ROMK is expressed throughout the DCT and into the cortical collecting duct. Expression of the epithelial Na^+ channel (ENaC), which mediates amiloride-sensitive Na^+ absorption, begins in the DCT2 and is expressed throughout the downstream connecting tubule and cortical collecting duct.

The DCT2 is the beginning of the aldosterone-sensitive distal nephron (ASDN) as identified by the presence of both the mineralocorticoid receptor and the enzyme 11β-hydroxysteroid dehydrogenase II. Importantly, this enzyme maintains the mineralocorticoid receptor free to only bind aldosterone by metabolizing

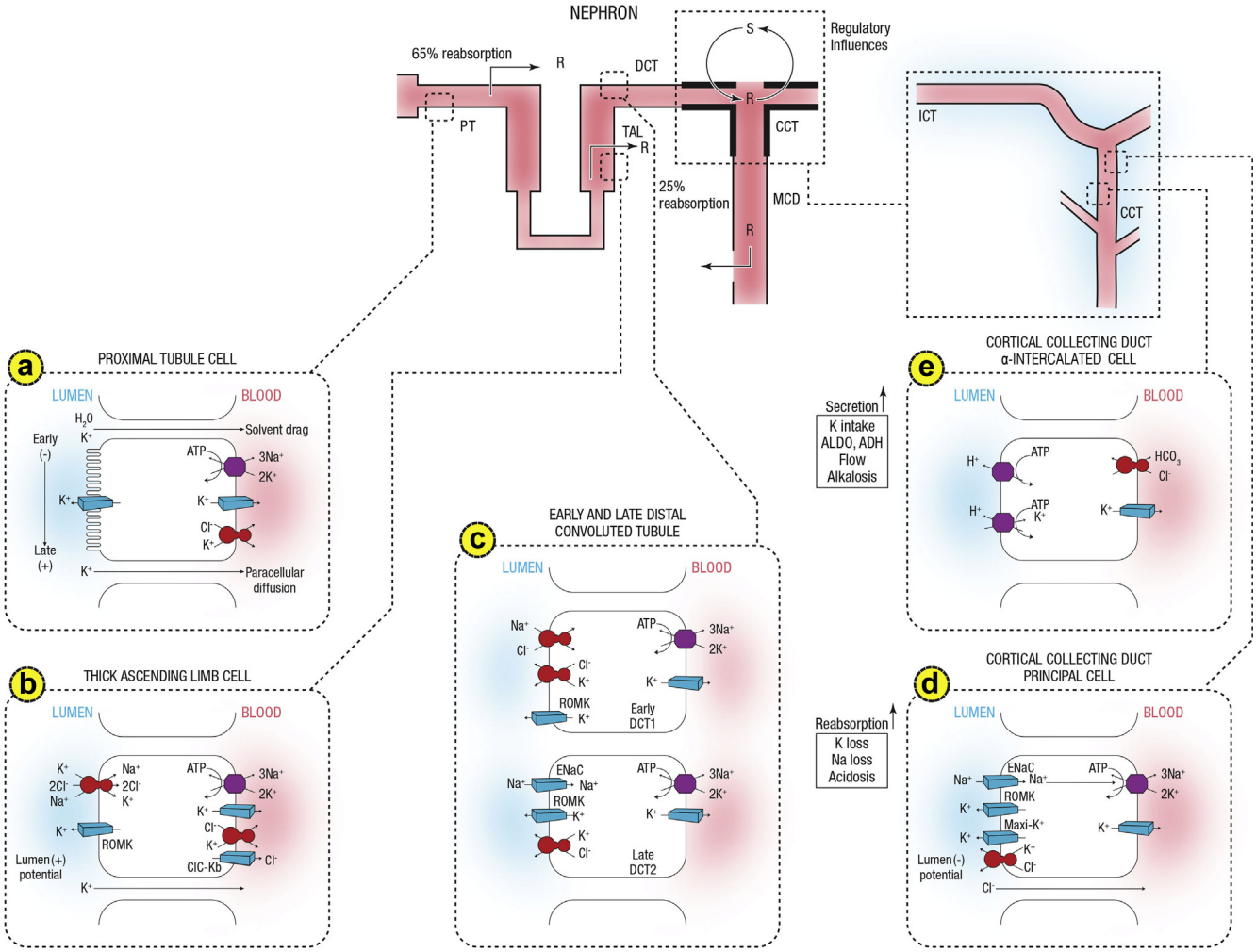

Figure 1. Summary of potassium transport along the nephron. Following filtration, potassium is extensively reabsorbed along the proximal tubule and the loop of Henle. Potassium is secreted along the initial and cortical collecting tubules. Net secretion can be replaced by net reabsorption in states of potassium depletion. Also shown are the 2 cell types lining the distal tubule and cortical collecting duct. (a) A cell model for K^+ transport in the proximal tubule. K^+ reabsorption in the proximal tubule primarily occurs through the paracellular pathway. Active Na^+ reabsorption drives net fluid reabsorption across the proximal tubule, which, in turn, drives K^+ reabsorption through a solvent drag mechanism. As fluid flows down the proximal tubule, the luminal voltage shifts from slightly negative to slightly positive. The shift in transepithelial voltage provides an additional driving force favoring K^+ diffusion through the low-resistance paracellular pathway. Experimental studies suggest that there may be a small component of transcellular K^+ transport; however, the significance of this pathway is not known. K^+ uptake through the Na^+-K^+-ATPase pump can exit the basolateral membrane through a conductive pathway or coupled to Cl^-. An apically located K^+ channel functions to stabilize the cell negative potential, particularly in the setting of Na^+-coupled cotransport of glucose and amino acids, which has a depolarizing effect on cell voltage. (b) A cell model for K^+ transport in the thick ascending limb of Henle. K^+ reabsorption occurs by both paracellular and transcellular mechanisms. The basolateral Na^+-K^+-ATPase pump maintains intracellular Na^+ at a low level, thus providing a favorable gradient to drive the apically located Na^+-K^+-$2Cl^-$ cotransporter (an example of secondary active transport). The apically located renal outer medullary K^+ (ROMK) channel provides a pathway for K^+ to recycle from cell to lumen, and ensures an adequate supply of K^+ to sustain Na^+-K^+-$2Cl^-$ cotransport. This movement through ROMK creates a lumen-positive voltage, providing a driving force for passive K^+ reabsorption through the paracellular pathway. Some of the K^+ entering the cell through the cotransporter exits the cell across the basolateral membrane, accounting for transcellular K^+ reabsorption. K^+ can exit the cell through a conductive pathway or in cotransport with Cl^-. ClC-Kb is the primary pathway for Cl^- efflux across the basolateral membrane. (c) A cell model for K^+ transport in the distal convoluted tubule (DCT). In the early DCT, luminal Na^+ uptake is mediated by the apically located thiazide-sensitive Na^+-Cl^- cotransporter. The transporter is energized by the basolateral Na^+-K^+-ATPase, which maintains low intracellular Na^+ concentration, thus providing a favorable gradient for Na^+ entry into the cell through secondary active transport. The cotransporter is abundantly expressed in the DCT1 but progressively declines along the DCT2. ROMK is expressed throughout the DCT and into the cortical collecting duct. Expression of the epithelial Na^+ channel (ENaC), which mediates amiloride-sensitive Na^+ absorption, begins in the DCT2 and is robustly expressed throughout the downstream connecting tubule and cortical collecting duct. The DCT2 is the beginning of the aldosterone-sensitive distal nephron as identified by the presence of both the mineralocorticoid receptor and the enzyme 11β-hydroxysteroid dehydrogenase II. This enzyme maintains the mineralocorticoid receptor free to only bind aldosterone by metabolizing cortisol to cortisone, which has no affinity for the receptor. Electrogenic-mediated K^+ transport begins in the DCT2 with the combined presence of ROMK, ENaC, and aldosterone sensitivity. Electroneutral K^+-Cl^- cotransport is present in the DCT and collecting duct. Conditions that promote a low luminal Cl^- concentration increase K^+ secretion through this mechanism, which occurs

(Continued)

cortisol to cortisone; the latter has no affinity for the receptor. Electrogenic-mediated K^+ transport begins in the DCT2 with the combined presence of ROMK, ENaC, and aldosterone sensitivity. Electroneutral K^+-Cl^- cotransport is present in the DCT and collecting duct. Conditions that cause a low luminal Cl^- concentration increase K^+ secretion through this mechanism, which occurs with delivery of poorly reabsorbable anions, such as sulfate, phosphate, or bicarbonate.

Principal cells exploit the electrochemical gradient established by sodium entry into the cell through a sodium channel at the luminal membrane (the molecular target of amiloride) and the basolateral membrane Na-K-ATPase to drive potassium secretion through 2 classes of luminal membrane potassium channels.[28] One of these, the renal outer medullary potassium (also termed ROMK) channels, secrete potassium under normal tubular fluid flow conditions and are inserted into or internalized from the luminal membrane, depending on the demand for potassium secretion. The other class of potassium channels is the so-called "big" conductance channels (known as BK channels), which are relatively inactive under normal conditions but exhibit increased activity during high tubular flow or high-potassium conditions.[28] The factors that regulate principal cell potassium secretion include previous potassium intake; intracellular potassium level; sodium delivery to the cells; urine flow rate; and hormones, such as aldosterone and catecholamines.[29] In contrast, the other collecting duct cell type, intercalated cells, mediate acid–base transport but upregulate expression of luminal H-K-ATPases during potassium depletion to enhance potassium reabsorption[25,30] (Figure 1).

To summarize, the kidney excretes sufficient milliequivalents of potassium to maintain total body homeostasis. Although the proximal nephron reabsorbs the bulk of the potassium filtered at the level of the glomerulus, it is a distal site, the collecting duct, that ultimately fine-tunes potassium excretion, thereby determining the final amount of potassium excreted in the urine. Consequently the collecting duct is the major site that responds to increased potassium intake, and in turn is subject to several regulatory influences.

Feedback Control of Potassium Balance

The classic feedback control of potassium is an exemplar of a homeostatic system that uses the consequence, or output, of a process to "feed back" and regulate the process itself. The feedback control of potassium is defined by the following stepwise cascade: In response to a high-potassium meal that includes glucose, pancreatic insulin secretion activates skeletal muscle and liver Na-K-ATPase, which moves potassium (Na/K exchange) from the plasma to the intracellular fluid of these cells. This mechanism minimizes the postprandial increase in plasma potassium concentration.[31] With muscle activity, potassium is released into the plasma and filtered at the glomerulus. In order to maintain balance, the amount of potassium consumed in the meal (minus the small amount lost in the feces) is excreted into the urine.

When an increase in potassium consumption increases plasma potassium concentration sufficiently, it triggers aldosterone synthesis and release from the adrenals, which stimulates the activity and synthesis of Na-K-ATPase and luminal potassium channels in collecting duct principal cells to secrete the excess potassium[32] (Figure 1). Aldosterone also enhances potassium excretion in the distal colon.[33] This latter function can be extremely important in the adaptation that occurs when renal function is compromised.

Conversely, if potassium intake is very low or urinary potassium excretory losses are excessive, plasma potassium concentration decreases and the feedback regulation is invoked, redistributing potassium from intracellular fluid to plasma thereby minimizing hypokalemia. Concomitantly skeletal muscle becomes insulin-resistant to potassium (but not glucose) uptake even before plasma potassium concentration decreases, which acts to blunt the shift of potassium from plasma into the cell.[34]

Figure 1. (Continued) with delivery of poorly reabsorbable anions, such as sulfate, phosphate, or bicarbonate. (d) The cell that is responsible for K^+ secretion in the initial collecting duct and the cortical collecting duct is the principal cell. This cell possesses a basolateral Na^+-K^+-ATPase that is responsible for the active transport of K^+ from the blood into the cell. The resultant high cell K^+ concentration provides a favorable diffusion gradient for movement of K^+ from the cell into the lumen. In addition to establishing a high intracellular K^+ concentration, the activity of this pump lowers intracellular Na^+ concentration, thereby maintaining a favorable diffusion gradient for movement of Na^+ from the lumen into the cell. The movements of both Na^+ and K^+ across the apical membrane occur through well-defined Na^+ and K^+ channels. (e) Reabsorption of HCO_3 in the distal nephron is mediated by apical H^+ secretion by the α-intercalated cell. Two transporters secrete H^+, a vacuolar H^+-ATPase and an H^+-K^+-ATPase. The H^+-K-ATPase uses the energy derived from ATP hydrolysis to secrete H^+ into the lumen and reabsorb K^+ in an electroneutral fashion. The activity of the H^+-K^+-ATPase increases in K^+ depletion and thus provides a mechanism by which K^+ depletion enhances both collecting duct H^+ secretion and K^+ absorption.[33] ADH, antidiuretic hormone; ALDO, aldosterone; ASDN, aldosterone-sensitive distal nephron; ATPase, adenosine triphosphatase; CCT, cortical collecting tubule; Cl, chloride; ClC-Kb, chloride channel Kb; DCT, distal convoluted tubule; ENaC, epithelial sodium channel; HCO_3, bicarbonate; ICT, initial connecting tubule; MCD, medullary collecting duct; PT, proximal tubule; R, reabsorption; ROMK, renal outer medullary potassium; S, secretion; TAL, thick ascending limb. Courtesy of Murray Epstein.

After hypokalemia ensues, the expression of skeletal muscle Na-K-ATPase α2 isoform decreases, which facilitates a net potassium "leak" from intracellular fluid to the plasma.[35] The low plasma potassium concentration suppresses adrenal aldosterone release; as a result the kidney can reclaim essentially all but about 1% of the filtered potassium (Figure 1). This renal potassium conservation involves downregulation of potassium secretion by means of the ROMK channels in cortical collecting duct principal cells. In conditions of potassium depletion, potassium reabsorption can occur in the collecting duct. This appears to be mediated by upregulation in the apically located H-K-ATPase on intercalated cells.[30]

What is of great interest is the realization that this intricate feedback mechanism for potassium regulation is not the sole mechanism for compensatory renal potassium excretion. Rather there is a complementary regulatory mechanism, a "feed-forward" control of potassium regulation, which acts in a complementary manner to subserve potassium homeostasis.

"Feed-Forward" Control of Potassium Balance

Although feedback loops are commonly recognized as regulators of biological systems, "feed-forward" loops of various sorts are also important biologic regulators. "Feed-forward" control refers to a pathway in a homeostatic system that responds to a signal in the environment in a predetermined manner, without responding to how the system subsequently reacts (that is, without responding to feedback). A widely recognized example of "feed-forward" control is the conditioned salivation of Pavlov's dogs in anticipation of food.[36] The Pavlovian conditioned salivary reflex is an example of a "feed-forward" regulatory loop in that a stimulus temporally associated with food (input) triggers salivation (output) in advance of presentation of food.[36]

Another intriguing example that has recently been proposed is closed "feed-forward" loops in which outputs that upregulate inputs also occur, leading to self-sustaining loops as in the case of a variety of intracrines.[37] Intracrine action permits the development of an active form of differentiation by which intracrines can spread from 1 cell to a target cell, upregulate intracrine action in that cell, and thereby establish a self-sustaining intracrine loop in that cell—a loop that will persist even when the extracellular intracrine is removed. An example is the recent observations that support the formulation of a "feed-forward" mineralocorticoid receptor–intracrine renin–angiotensin system interaction irrespective of whether aldosterone or another moiety activates the mineralocorticoid receptor in diverse disease states.[37]

With this theoretical construct as context, we will now consider the formulation of another recent example of "feed-forward" control that is highly relevant and of great immediacy—the "feed-forward" control of potassium. By analogy, a similar "feed-forward" control mechanism is involved in potassium homeostasis. In describing this regulatory loop, a caveat is in order. It is a truism that any mechanism for homeostatic regulation cannot be called "feedback" or "feed-forward" until the details of regulation have been delineated. In the case of the feedback system for K^+ regulation, which has been described above, these details are well defined. As will be apparent in the following sections, the details of the "feed-forward" regulatory mechanism have not been fully defined; neither the locus nor the molecular nature of the receptors nor even the signals between the kidney and the gastrointestinal (GI) tract have been elucidated. Consequently, for the purposes of our discussion in describing the phenomenology, we will refer to this homeostatic mechanism as "feed-forward" (with quotes), fully conceding that the mechanistic details await elucidation.

The "feed-forward" control mechanism subserving potassium homeostasis posits that even minor changes in dietary potassium intake, which are insufficient to alter plasma concentrations of either potassium[38] or aldosterone,[39] and consequently insufficient to activate feedback control, are capable of evoking rapid changes in renal potassium excretion through "feed-forward" mechanisms (Figure 2).

Thirty years ago, Rabinowitz and associates[40] conducted a serious of elegant experiments in sheep, which demonstrated that potassium intake in food or potassium placed into the rumen (sheep stomach) was associated with a large and significant increase in urinary potassium excretion. Although others[41,42] had earlier demonstrated that feeding was associated with an increase in urinary potassium excretion, Rabinowitz *et al.*[40] designed a series of 13 experiments to explore the known factors that regulated urinary potassium excretion to determine which of them might contribute to this effect. They showed that the increase in urinary potassium excretion was not related to an increase in serum potassium or glomerular filtration rate and thus the increase in urinary potassium excretion was not a consequence of an increase in filtered potassium, but rather tubular potassium excretion. They demonstrated that aldosterone was not responsible for this by either (i) showing there was no change in plasma aldosterone concentration, (ii) infusing aldosterone and showing it did not alter the effect, or (iii) giving an early aldosterone antagonist (potassium canrenoate), which also did not alter the

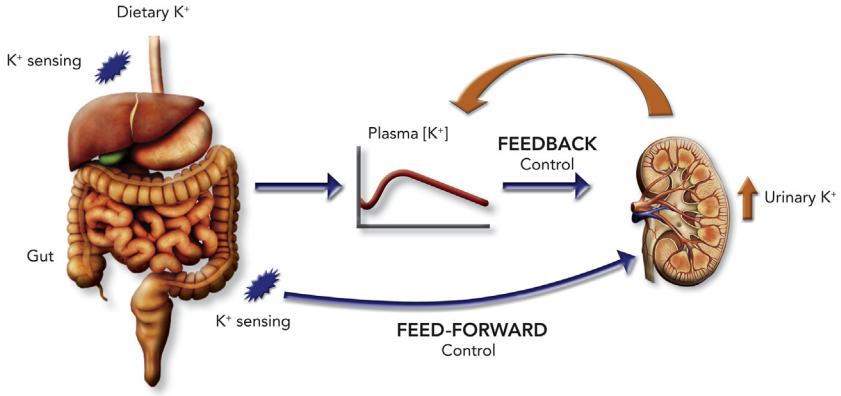

Figure 2. A schematic depicting the complementary roles of the classic feedback and "feed-forward" control mechanisms for maintaining potassium homeostasis. An increase in plasma potassium evokes an array of responses that promote a kaliuresis. In contrast, the "feed-forward" control mechanism is engaged when dietary potassium is sensed by K^+ sensors in the gastrointestinal tract in the absence of perceptible changes in plasma potassium. Courtesy of Murray Epstein.

effect. Similarly, when urine flow rate or sodium excretion was altered or urine pH was altered, the effect persisted. They concluded as follows: "The efferent factors involved in this regulation remain to be determined. They do not appear to be aldosterone, urine flow, sodium excretion, or acid/base status, nor do changes in plasma potassium appear to be necessary or sufficient to produce the changes in potassium excretion associated with meal intake or fasting." They stated "that there was a correlation between changes in rumen fluid potassium concentration and renal potassium excretion." They concluded that their studies were "compatible with the presence of receptors located at some point prior to the systemic circulation, which sense enteric potassium levels and influence renal potassium excretion" (Figure 3).

Numerous studies have subsequently been conducted (i) to confirm these findings in additional species, including humans, (ii) to try to determine the location for this putative potassium sensor, and (iii) to evaluate potential signals that might increase renal potassium excretion.

Studies in Different Species to Confirm That an Effect of Potassium Administration Into the GI Tract Directly Leads to an Increase in Renal Potassium Excretion

Lee *et al.*,[43] Oh *et al.*,[44] and Morita *et al.*[45] conducted studies in anesthetized rats with findings consistent with those of Rabinowitz *et al.*[40] Calo *et al.*[38] found qualitatively similar findings in humans. In these human studies, during a water diuresis, intake of potassium led to an increase in urinary potassium excretion within 20 minutes, at a time when neither plasma potassium nor aldosterone had increased.

Recently Preston *et al.*[46] conducted studies to further delineate this GI–renal kaliuretic signaling axis in 32 normal subjects in a clinical research unit while on a 20-mmol sodium and 60-mmol potassium diet. The serum potassium concentration, potassium excretion, aldosterone, and insulin were measured following either a 35-mmol oral potassium load, a potassium- and sodium-deficient complex meal, or a potassium-deficient complex meal plus 35 mmol potassium. This experimental design facilitated determination of the

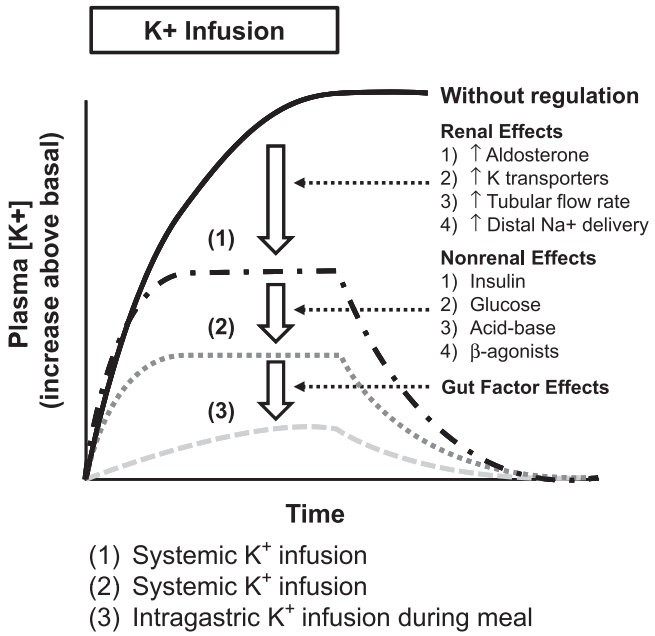

Figure 3. Summary of the integrated roles of the kidney, extrarenal mechanisms, and gastrointestinal effectors in modulating potassium homeostasis. It demonstrates that the undamped increase in plasma K^+ in response to potassium administration is progressively attenuated by the adaptive responses by the kidney, by a hierarchy of nonrenal mechanisms including participation by insulin and glucose, and by gastrointestinal mechanisms evoked by gastrointestinal potassium sensors.[33] Courtesy of Murray Epstein. Adapted with permission from Youn JH. Gut sensing of potassium intake and its role in potassium homeostasis. *Semin Nephrol.* 2013 May;33:248–256. Copyright © 2013, Elsevier Inc.

component effects on potassium handling of the meal and potassium load separately. The meal plus potassium test was repeated following aldosterone blockade achieved with eplerenone treatment in order to specifically evaluate the role of aldosterone. In response to the potassium-deficient meal plus 35 mmol potassium, the serum potassium did not increase but the hourly mean potassium excretion increased sharply. This kaliuresis persisted following aldosterone blockade with eplerenone, thereby suggesting independence from aldosterone. The authors concluded that this experiment further substantiated the existence of a GI–renal kaliuretic signaling axis in humans that is capable of mediating potassium excretion independent of changes in the serum potassium concentration and aldosterone.

Studies Designed to Determine the Location for the GI Potassium Sensor

The original studies by Rabinowitz and colleagues[39,40] involved direct administration of potassium into the rumens of sheep. Morita and colleagues[45,47] suggested the sensor might be in the hepatoportal area, whereas Lee *et al.*[43] indicated that the stomach and not the portal circulation was more important. In Morita's studies, intraportal infusion of potassium led to a greater renal potassium excretion than did an i.v. infusion. Cutting the periarterial hepatic nervous plexus diminished the increase in urinary potassium excretion. In addition, potassium infused directly into the hepatoportal circulation stimulated hepatic afferent nerve activity and increased urinary potassium excretion without changes in plasma potassium.

Studies Designed to Determine the Potential Signal(s) That Might Increase Renal Potassium Excretion

Oh *et al.*[44] evaluated a number of GI hormones to test whether they might be responsible for the increase in renal potassium excretion. They evaluated guanylin, uroguanylin, glucagon-like peptide, and extraintestinal hormones such as arginine vasopressin, α- and γ-melanocyte-stimulating hormone, and aldosterone. Their data do not support a role for these hormones in this phenomenon, leading them to suggest that there might be "previously unknown humoral factors that stimulate renal K^+ excretion during dietary K^+ intake."

Although not a GI hormone, the renal kallikrein–kinin system is activated by high-K^+ diet or acute K^+ loading leading to an increase in urinary tissue kallikrein.[48] El Moghrabi *et al.*[49] showed, in mice, that renal tissue kallikrein can lead to an increase in renal potassium excretion by both activating the epithelial Na channel to increase K^+ excretion by principal cells and inhibiting H-K-ATPase in intercalated cells to decrease K^+ reabsorption. Renal K^+ excretion increased in concert with tissue kallikrein excretion following a single meal. They further showed that in tissue kallikrein knockout mice there was a greater increase in serum potassium following a meal, suggesting that tissue kallikrein plays a role in renal potassium excretion. Thus, although renal tissue kallikrein is not a GI-derived signal, it could play a role in this phenomenon at the level of the kidney.

The studies of Sorensen *et al.*[50] may be relevant in further considering mechanisms that are operative at the level of the kidney. They studied mice and found that an acute intragastric potassium load led to rapid dephosphorylation of the renal sodium chloride cotransporter (NCC), which was associated, as would be predicted, with an increase in sodium and potassium excretion. Sorensen *et al.*[50] showed that this effect was independent of aldosterone.

Although glucagon is also a circulating hormone that acts on the kidney to increase electrolyte excretion, including potassium, it is unlikely to play a role. Glucagon acts at the level of the proximal tubule, and its potential role as a mediator of the kaliuresis invoked by an oral potassium load has not been delineated.

Physiological Observations of Sodium That May Serve as an Analogous Template for K^+

Several lines of experimental evidence, focusing on sodium homeostasis, constitute a template for the concept that a "feed-forward" mechanism with sensors in the GI area, the hepatosplanchnic area, or both areas participates in potassium homeostasis. Sensing the amount of ingested sodium is 1 mechanism by which sodium balance is regulated. In a seminal paper published almost 40 years ago, Carey[51] reported that the rapidity of renal sodium excretion in response to an administered sodium load differs depending on the route of administration; an oral sodium load is excreted more rapidly than an identical sodium load administered intravenously. Neural mechanisms[52] and gut hormones (e.g., uroguanylin [Guca2b], cholecystokinin) have been proposed to mediate the natriuresis of an oral sodium load.

The natriuresis following ingestion of a certain amount of sodium may be due to the enterokine gastrin, which is secreted by G cells in the stomach and duodenum and released into the circulation.[53,54] Gastrin is taken up by renal cortical tubules to a greater extent than the other enterokines released after a meal.[55] Gastrin then acts on its receptor, the cholecystokinin B receptor (CCKBR), expressed in several nephron segments[54,56] to alter sodium transport.

Additional Determinants of Renal Potassium Excretion

Circadian Rhythm of Potassium Excretion

The presence of circadian rhythms that characterize renal function and excretion has been documented for over 60 years.[57,58] Kidney parameters with such rhythms include glomerular filtration rate, renal plasma flow, and tubular reabsorption and secretion for most of the major urinary electrolytes. Of interest for the focus of this Review is the demonstration of a circadian rhythm that characterizes renal potassium excretion in humans, with a peak in the middle of the day.[59] This pattern is independent of activity, posture, and dietary intake; this circadian rhythm persists for days in individuals, and it is isolated from most external cues.

Originally this pattern of renal potassium excretion was thought to be driven by factors mainly external to the kidney. Recent studies, however, have demonstrated rhythms within the tubule, which would account for many of these changes. Steele *et al.*[60] suggested that transtubular potassium gradients could be the driving force for the cycles in potassium excretion. Zuber *et al.*[61] demonstrated rhythmicity in transcripts from cells of the rat distal nephron (distal convoluted tubule/connecting tubule and cortical collecting duct) in potassium channels such as ROMK1, KCNK1, and KCNJ10. Their finding of ROMK1 cycling by about 30% at the mRNA level might explain part of the circadian variation observed in renal potassium excretion. Finally, since aldosterone is acknowledged to play a critical role in renal potassium excretion, the demonstration of a circadian rhythm in aldosterone secretion[62] and its consequent effects at the level of the tubule[63] allow for the possibility that cycles in renal potassium excretion could be controlled both by cycles outside the kidney such as aldosterone and by cycles within the kidney tubules themselves.

Posture and Potassium Excretion

Several studies conducted 60 years ago found little or no effect of posture on renal potassium excretion.[64] "Posture had comparatively little prolonged effect on absolute potassium excretion when allowance was made for diurnal rhythmic variations."[65] "Change of posture usually produced less disturbance of the diurnal rhythm in potassium excretion, and changes in potassium excretion (urinary K^+) were usually small in comparison with those in sodium output."[66] In summary, posture can exert a considerable effect on urine flow rate and sodium excretion, but the available data suggest that changes in potassium excretion are relatively small.

GI Potassium Absorption and Excretion

As indicated above, stool potassium usually averages about 10% of ingested potassium. Thus, on a standard Western diet with approximately 80 mEq of potassium, this would regularly lead to approximately 8 mEq of potassium in the stool.[25,26] In normal individuals, the large fraction of ingested potassium is absorbed by the small intestine, and the contribution of the normal colon to net potassium absorption or secretion is small.[67] Potassium transport in the duodenum, jejunum, ileum, and colon has been characterized as passive absorption, although the colon also demonstrates passive secretion.[53,67] Colonic potassium secretion exists in mammals[68] and has been shown to play a role in potassium homeostasis in patients on dialysis.[69] Administration of mineralocorticoids leads to small but significant increases in stool potassium excretion.[67,70] Factors that might lead to an increase in stool potassium have been reviewed,[71] and are briefly summarized.

The Role for the Liver in Subserving Potassium Homeostasis

Recently Halperin's group[72] proposed an engaging new formulation suggesting a pivotal role for the liver in subserving potassium homeostasis. They suggested that lactate augmented potassium uptake by the liver. Studies were conducted in normal rats compared with rats with acute hyperkalemia. There was a significant fall in plasma K^+ in normal rats and an even larger fall in plasma K^+ in both models of acute hyperkalemia when the plasma L-lactate rose, caused by a shift of K^+ from cells, or by a positive K^+ balance. A rise in the plasma L-lactate in portal venous blood led to a fall in the plasma K^+, and insulin was permissive. Interestingly, studies conducted to delineate the time course for changes in the plasma K^+ in normal rats disclosed that plasma K^+ fell significantly to its nadir within the first 15 minutes, and it remained close to this level for the next 30 minutes.

The investigators suggested that absorption of glucose by the Na^+-linked glucose transporter permits enterocytes to produce enough adenosine diphosphate to augment aerobic glycolysis, raising the plasma L-lactate in the portal vein, thereby preventing postprandial hyperkalemia. Overall, the integrative physiology of this proposed regulatory process provides a rationale for having SLGT-1 in enterocytes—the release of L-lactic acid into the portal vein—and proposes a central role for the liver to minimize the risk of having a large rise in the plasma K^+ delivered to the heart following the ingestion of K^+.

Colonic Potassium Handling

Relatively recent studies in rodents, over the past 2 decades, have further defined the intricacies of

mammalian colonic K^+ handling.[71] One important basic aspect of K^+ transport in the colon is its segmental difference. Under normal conditions, the proximal colon performs net K^+ secretion while net K^+ absorption is observed in the distal colon. The proximal colon does not absorb K^+ actively. Active K^+ absorption in the distal colon occurs via the transcellular route and involves a primary active K^+ entry step across the apical membrane. In the mammalian distal colon this active transport is conducted by the non-gastric H-K-ATPase localized in surface cells of the distal colon. Mice with this H-K-ATPase knocked out maintain a normal serum K^+ when fed a normal diet, but become hypokalemic on a low-K^+ diet. Thus, this H-K-ATPase plays a critical role in colonic K^+ absorption.

Net K^+ secretion is found in both the proximal colon and distal colon in animals fed a high-K^+ diet. Present evidence suggests that net K^+ secretion is carried out by K^+ channels. Although there are several potential K^+ channels that could perform this function, BK channels seem to be the only functionally significant K^+ secretory ion channel in the apical membrane of the distal colon.[71] The role of the colon in clinically modulating K^+ excretion is not adequately recognized. Early studies in end-stage renal disease found that the colon was responsible for a small but significant increase in K^+ excretion.[73] Over a number of years these findings have been confirmed[74,75] and in recent times have been attributed to an increase in BK channel activity.[76] This being the case, it might seem attractive to try to develop pharmacologic agents that could be used to stimulate BK potassium channel activity. If such an agent were to exist, it could have clinical utility in settings of hyperkalemia, particularly where oral intake might be limited and thus potassium binding agents might not be useful.

In patients without renal disease, large-volume diarrhea has historically been attributed to Cl secretion with Na following the Cl, and little K^+ is found in these stools.[77] van Dinter *et al.*, including John Fordtran, reported on a well-studied woman with secretory diarrhea in the setting of colonic pseudo-obstruction in which K^+ secretion seemed to be responsible for the diarrhea with stool K^+ averaging 154 mEq/l and serum K^+ frequently being below 3.5 mEq/l.[78] In that same report they indicated that they were aware of 3 other patients with similar findings. Following this report, the group in Leeds, Sandle's group, reported a patient with secretory diarrhea following hemorrhagic shock[79] with high levels of K^+ in the stool and histologic evidence of "massive over-expression of BK channel protein in colonic crypts." In a subsequent review this same group[80] reported evidence for potassium (BK) channels being responsible for increased stool K^+ in patients with ulcerative colitis, colonic pseudo-obstruction, laxative abuse with bisacodyl, and renal failure. Thus, they suggest that in all these settings increased K^+ excretion in the stool, including up to levels of over 150 mEq/l, could all be mediated by increased BK channel activity.

As mentioned earlier, normal individuals on a normal diet absorb virtually all ingested K^+, and most of this ingested K^+ is excreted in the urine. Importantly, in the setting of chronic kidney disease, and in particular chronic dialysis patients, colonic K^+ secretion is greatly enhanced and becomes an important accessory K^+ excretory pathway.[69] The imminent clinical availability of 2 new polymer potassium binders, patiromer and sodium zirconium cyclosilicate, that modulate their effects in large part in the colon has further emphasized the importance of increasing our understanding of the physiology of colonic potassium handling.

Potassium Binding in the GI Tract

The Evolving Role of Potassium-Binding Resins in Hyperkalemia

Because of the widely documented array of complications of hyperkalemia, determination of hyperkalemia constitutes an "action item" for the clinician. Most clinicians feel compelled to respond vigorously to hyperkalemia. As detailed in several recent reviews, hyperkalemia may be an immediately life-threatening condition.[81–84] Severe hyperkalemia can cause ventricular fibrillation or asystole, unless extracellular potassium is reduced.[81] Even relatively mild (5.5–6.0 mEq/l) hyperkalemia is associated with an increased risk of mortality within the next 24 hours, even without electrocardiogram changes.[81] Because of these well-recognized associations, clinicians feel compelled to intervene and respond vigorously to hyperkalemia.

As detailed earlier, the majority of potassium is renally excreted, but about 5% to 10% is secreted in the colon. Because potassium is regularly excreted in the stool and since that process could potentially be augmented by cation exchange resins, such treatment could lead to an increase in stool potassium excretion. Treatment with exchange resins has been used in the management of clinical hyperkalemia for over 60 years. The most commonly used resin to date has been sodium polystyrene sulfonate (SPS) (Kayexalate). However, the utility and safety of SPS in the treatment of hyperkalemia is currently being challenged. Several investigators have questioned the effectiveness of SPS in lowering serum potassium levels.[85]

As of the writing of this article (November 2015), several of the agents that we currently use for the treatment of acute hyperkalemia are unproven with respect to efficacy as judged by currently mandated

criteria—but it is reasonable to aver that the majority clinical consensus is that they do work.[86]

SPS potassium-binding resins (Kayexalate, Kionex, and others), with and without an associated cathartic (usually sorbitol), have been in use for almost 60 years and are approved by the US Food and Drug Administration (FDA) for the treatment of hyperkalemia. In September 2009, the FDA recommended against the "concomitant use of sorbitol" with Kayexalate powder because of associated cases of colonic necrosis and other severe GI side effects.[87] However, this warning did not apply to premixed SPS in 33% sorbitol for oral use (various manufacturers), the only SPS resin that is currently available in many hospitals.

SPS potassium-binding resins work by increasing colonic potassium excretion. In hyperkalemic patients, oral SPS mixed in water significantly decreases serum potassium within 24 hours. Colonic necrosis associated with SPS and sorbitol is most commonly seen in patients who have received enemas in the setting of recent abdominal surgery, bowel injury, or intestinal dysfunction. The agent most likely associated with colonic necrosis is 70% sorbitol, and animal data support that etiology. There are very few data to suggest that oral SPS given with 33% sorbitol (in the premixed form) or SPS powder in water orally or as an enema causes colonic necrosis.

In 2010, Sterns *et al.*,[85] in an editorial review, concluded that SPS resins are "largely unproven and potentially harmful," especially when administered with sorbitol, and that clinicians should "exhaust other alternatives." Some investigators objected to the condemnation and stated that these conclusions are immoderate.[86,88] When indicated, and in patients who have no contraindication to their use, SPS resins are effective and reasonably safe.

In light of these considerations, what might constitute the "therapeutic niche" for SPS? Watson *et al.*[86] have appropriately highlighted an important role for SPS in the treatment of acute hyperkalemia under dire and challenging conditions after a natural or man-made disaster.[89,90] It may be used for trauma-associated hyperkalemia and as prophylaxis in dialysis-dependent patients who are not able to get to a dialysis unit.[89,90] Everyday examples that the readers can readily relate to include the recent mid-Atlantic blizzard of 5 to 6 February 2010, commonly referred to as Snowmageddon or Snowpocalypse, a category 3 ("major") nor'easter and severe weather event, when many chronic dialysis patients were unable to be transported to their dialysis units. Additional examples include the aftermath of Hurricane Katrina and after the Haitian earthquake.[91] In such situations where dialysis availability is limited, SPS may be the only option for potassium removal in hyperkalemic patients, especially chronic dialysis patients.

We wish to stand back from this ongoing controversy and share a few thoughts and recommendations. Unrelated to the controversy of SPS's efficacy, and how frequently colonic necrosis may supervene, it is readily apparent that the administration of SPS is fraught with additional challenges related to its administration and patient discomfort. These considerations set the stage for the imminent availability of the newer efficacious and "patient-friendly" potassium binders—patiromer and sodium zirconium cyclosilicate (ZS-9).

Patiromer was approved by the FDA for the treatment of hyperkalemia on 21 October 2015. ZS-9 is currently in the late stages of clinical development and is expected to be approved and in clinical use shortly. These agents may offer advantages over existing approaches to hyperkalemia treatment. Both patiromer and ZS-9 act to remove potassium by exchanging cations (calcium for patiromer and sodium for ZS-9) for potassium in the distal colon, binding potassium, and increasing its fecal excretion.[4–7] Patiromer is an organic, non-absorbed polymer that increases fecal potassium excretion by exchanging potassium for calcium primarily in the distal colon. It is a free-flowing, insoluble powder of small (~100 μm) spherical beads with low viscosity.[6,7] ZS-9 is an inorganic polymer, which selectively attracts potassium ions to its negatively charged crystalline lattice structure and exchanges them for sodium and hydrogen. It is formulated as a free-flowing, insoluble powder that is not absorbed systemically.[92]

As of this writing, multiple clinical trials have demonstrated the safety and efficacy of both binders in diverse disease states including congestive heart failure, chronic kidney disease, diabetic nephropathy, and, in a preliminary study, resistant hypertension.[93] The reader is referred to the article by Weir in *Kidney International Supplements*[94] for a detailed summary and analysis of these clinical trials.

In summary, it appears that there will be 2 new products available in the near future to facilitate the management of hyperkalemia in patients with chronic and recurrent hyperkalemia. Patiromer (Valtessa) was approved by the FDA for a broad indication of "treatment of hyperkalemia." ZS-9 is in the latest stages of clinical development but not yet approved. These agents may offer to serve as "enablers" facilitating treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists in optimal recommended doses, obviating down-titration and discontinuation of these life-saving treatments.

Conclusions

The integrated mechanisms controlling the maintenance of potassium homeostasis are well established

and are defined by the classic "feedback control" of potassium balance. This "feedback control" of potassium homeostasis has long constituted the platform for defining therapeutic interventions for the management of hyperkalemia. This relatively straightforward theoretical construct has recently been amplified by a wide array of physiological studies. In recent years, increasing investigative attention has focused on novel physiological paradigms that increase the complexity but also the precision of homeostasis—the "feed-forward" control of potassium balance. The elegant studies of Rabinowitz and associates over 3 decades ago have very recently been confirmed in human subjects by the well-defined studies of Preston and associates. Subsequent physiological studies have been conducted in an effort to determine both the location for the GI potassium sensor and the potential signal(s), which might increase renal potassium excretion. Concomitant studies in animal models have further defined the intricacies of mammalian colonic K^+ handling. In concert these investigative efforts have increased both the complexity but also the precision of homeostasis, with a resultant enhanced investigative interest in potassium.

These new insights are relevant to the future design of clinical trials delineating renal potassium handling. As an example, the insights regarding "feed-forward" control of potassium mandate that the conditions of study, especially attention to standardization of the fasting or fed state of subjects, are a requisite for the trial design. A recent study has demonstrated that imposition of rigorous dietary potassium intake serves to reduce variability in serum potassium levels.[95]

Finally, the demonstration of massive overexpression of BK channel protein in "colonic crypts," and evidence for potassium (BK) channels being responsible for increased stool K^+ in some patients with diseases such as ulcerative colitis, introduce interesting therapeutic speculations. As an example, it may be attractive to attempt to develop pharmacologic agents that could be used to stimulate colonic BK potassium channel activity. If such an agent were to exist, it could have clinical utility in settings of hyperkalemia, particularly where oral intake might be limited and thus potassium binding agents might not be useful. The next few years should be rewarding concerning the wide array of physiological and clinical investigations of potassium homeostasis based on the recent insights and discoveries detailed in this Review.

DISCLOSURE

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