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PERSPECTIVES IN RENAL MEDICINE

Hyperkalemia: An adaptive response in chronic renal insufficiency

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Hyperkalemia: An adaptive response in chronic renal insufficiency.

Background. Hyperkalemia is a common feature of chronic renal insufficiency, usually ascribed to impaired K^+ homeostasis. However, various experimental observations suggest that the increase in extracellular $[K^+]$ actually functions in a homeostatic fashion, directly stimulating renal K^+ excretion through an effect that is independent of, and additive to, aldosterone.

Methods. We have reviewed relevant studies in experimental animals and in human subjects that have examined the regulation of K^+ excretion and its relation to plasma $[K^+]$.

Results. Studies indicate that (*1*) extracellular $[K^+]$ in patients with renal insufficiency correlates directly with intracellular K^+ content, and (*2*) hyperkalemia directly promotes K^+ secretion in the principal cells of the collecting duct by increasing apical and basolateral membrane conductances. The effect of hyperkalemia differs from that of aldosterone in that K^+ conductances are increased as the primary event. The changes in principal cell function and structure induced by hyperkalemia are indistinguishable from the effects seen in adaptation to a high K^+ diet.

Conclusions. We propose that hyperkalemia plays a pivotal role in K^+ homeostasis in renal insufficiency by stimulating K^+ excretion. In patients with chronic renal insufficiency, a new steady state develops in which extracellular $[K^+]$ rises to the level needed to stimulate K^+ excretion so that it again matches intake. When this new steady state is achieved, plasma $[K^+]$ remains stable unless dietary intake increases, glomerular filtration rate falls, or drugs are given that disrupt the new balance.

Hyperkalemia in chronic renal insufficiency is generally viewed as a sign of impaired potassium homeostasis, usually ascribed to toxic effects on cell membrane Na^+, K^+-ATPase pump activity or to hyporeninemic hypoaldosteronism [1–4]. In this review, we propose that hyperkalemia is not due to a failure in homeostasis, but rather is a physiological success story. Evidence is presented indicating that hyperkalemia is associated with an increase rather than a maldistribution in body K^+ stores, and that it promotes K^+ excretion by directly stimulating K^+ secretion in the principal cells of the collecting duct of the kidney. Based on such evidence, we postulate that hyperkalemia in renal insufficiency is an adaptive change that serves to restore K^+ balance in the face of a reduction in functioning nephrons. This "K^+ adaptation" is the key to establishing a new homeostatic set point at which K^+ excretion again matches intake. In addition, it may provide protection against surges in plasma $[K^+]$ that might otherwise occur in chronic renal insufficiency.

Key words: hyperkalemia, potassium, potassium adaptation, kidney, renal failure, ROMK.

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INCIDENCE OF HYPERKALEMIA IN RENAL INSUFFICIENCY

The incidence of hyperkalemia in patients with chronic renal insufficiency is difficult to assess because of the almost universal use of drugs that influence plasma $[K^+]$. In one study carried out before angiotensin-converting enzyme (ACE) inhibitors were available and which excluded patients receiving diuretics, plasma $[K^+]$ was significantly elevated (average value, 4.9 mmol/L) even in patients with only mild-moderate renal dysfunction (serum creatinine 2 to 4 mg/dL) [5]. Hyperkalemia appears to occur more frequently in patients with tubulointerstitial disease or diabetes mellitus [6, 7], but is clearly not confined to these disorders [6]. In a random sample of 300 patients with serum creatinine levels of 1.5 to 6.0 mg/dL taken from our clinic, excluding individuals with diabetes and those receiving either diuretics or drugs that impair angiotensin II synthesis or effect, we found an incidence of hyperkalemia (plasma $[K^+]$ 5.0 mmol/L or higher) of 55%. In the small group of patients in this sample meeting our criteria for inclusion ($N = 18$, mean serum creatinine, 3.1 mg/dL), hyperkalemia was as likely to occur with glomerular diseases as with tubulointerstitial disease. Based on these limited observations, the prevalence of hyperkalemia in patients with renal insufficiency may exceed 50%.

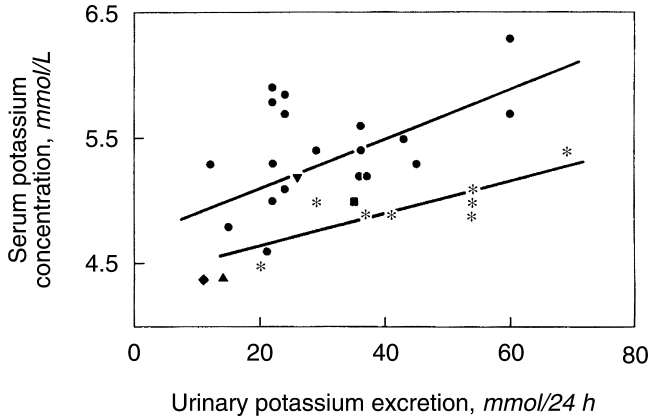

Fig. 1. Relationship between plasma [K^+] and urine K^+ excretion in patients with chronic renal insufficiency. The solid symbols and upper regression line are data obtained in patients with low renin and aldosterone levels; the asterisks and lower regression line are data obtained in patients with normal renin and aldosterone levels. Reprinted with permission from the International Society of Nephrology [7].

POTASSIUM HOMEOSTASIS IN RENAL INSUFFICIENCY

Regardless of whether hyperkalemia is present in the steady state, patients with renal insufficiency have a diminished ability to acutely excrete a K^+ load and, therefore, have more severe and prolonged hyperkalemia when challenged [8, 9]. Because hyperkalemia stimulates aldosterone secretion, one might expect aldosterone levels to be higher in patients with renal insufficiency than in individuals with normal renal function. However, aldosterone measurements have shown widely varying patterns [3, 7, 10–12], and its importance as a factor in maintaining K^+ balance in renal insufficiency is uncertain. In patients with renal insufficiency, plasma [K^+] has been shown to correlate directly with daily urinary K^+ excretion regardless of the circulating aldosterone level [7]. In this carefully studied group of patients, those with the highest plasma [K^+] had the greatest urinary K^+ excretion (Fig. 1). Assuming these patients are in K^+ balance, those with the highest excretion must also have had the highest dietary K^+ intake.

In a related study, K^+ intake was deliberately increased in patients with stable chronic renal insufficiency (mean creatinine clearance, 30 mL/min) by giving them a K^+ supplement of 50 mmol/day [13]. The patients with renal insufficiency increased K^+ excretion to the same degree as control subjects given the same supplement but, in contrast to the control subjects, achieved this goal by increasing plasma [K^+] by 0.7 mmol/L, to a mean value of 5.4 mmol/L. These observations suggest a causal linkage between the increase in plasma [K^+] and stimulation of renal K^+ excretion. The respective roles of extracellular [K^+], aldosterone, and other factors in maintaining K^+ balance in renal insufficiency are discussed in detail below.

TRANSCELLULAR POTASSIUM HOMEOSTASIS IN RENAL INSUFFICIENCY

Before reviewing the regulation of K^+ excretion in patients with chronic renal insufficiency, it is important to address the issue of whether the hyperkalemia seen in these patients is due to impaired entry of K^+ into cells or reflects an increase in intracellular K^+ stores. Two general approaches—measurement of total body or striated muscle K^+ stores, and assessment of cell membrane Na^+, K^+-ATPase activity or function—have been used to address this issue. Both approaches have limitations and have provided conflicting results. The key studies are discussed below.

Body potassium stores

Measurements of total body K^+ content in patients with renal insufficiency show low or normal values, a finding advanced to support the view that K^+ entry into cells is impaired [14–22]. It should be emphasized, however, that these measurements give little information about intracellular K^+ content [14, 22]. Total body stores will be reduced compared to normal individuals, for example, if there is a loss of muscle mass (the main reservoir of intracellular K^+) due to uremia, even though intracellular K^+ in the remaining muscle cells may be normal or increased [16, 23]. A more direct assessment of intracellular K^+ can be obtained by analyzing the K^+ content of striated muscle obtained in biopsy samples. Such measurements have shown, in most instances, that the K^+ content in muscle tissue in patients with even advanced renal insufficiency is either indistinguishable from individuals with normal renal function or increased [14, 19, 20].

Correlation between extracellular and intracellular [K^+]

The key issue of whether extracellular [K^+] correlates directly with intracellular [K^+] has been addressed in a systematic fashion in only one study [19]. In this study, in which the K^+ content of muscle samples was assessed in patients with renal insufficiency (serum creatinine range, 3.6 to 19.5 mg/dL), plasma [K^+] correlated directly with muscle K^+ content (Fig. 2). The authors found an even stronger correlation between plasma and intracellular [K^+] when they estimated the latter from the ratio of K^+ content to water content. Therefore, hyperkalemia is associated both with a higher muscle K^+ content and a higher intracellular K^+/H_2O ratio.

Assessment of ATPase activity and function

In red cells, white cells, and myocytes taken from patients and experimental animals with renal insufficiency, Na^+,K^+-ATPase activity is consistently decreased compared to normal controls [1, 2, 4, 24–26]. However, when Na^+, K^+-ATPase function is tested in animals and hu-

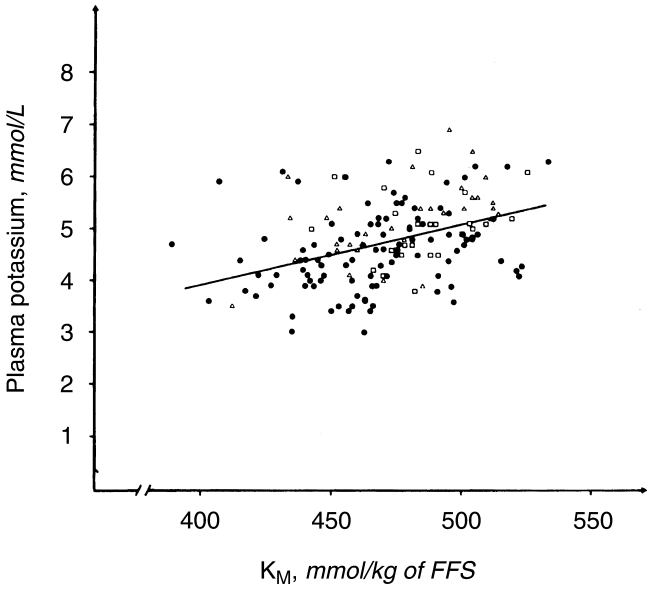

Fig. 2. Relationship between plasma [K^+] and muscle K^+ content in 103 patients with renal insufficiency. Muscle K^+ content (K_M) is given in mmol/kg of fat-free solids (FFS). The closed symbols are samples taken from patients not receiving dialysis therapy, and the open symbols are from patients receiving either peritoneal or hemodialysis therapy. Reprinted with permission from the International Society of Nephrology [19].

mans with renal insufficiency, no abnormality is detected. Stimulation of Na^+,K^+-ATPase activity by either insulin or K^+ administration, assessed by K^+ entry into cells, is not impaired [6, 8, 9, 26, 27]. In one study, K^+ entry into cells in response to insulin was actually greater in uremic rats than in normal controls [26]. The reason for the decrease in Na^+,K^+-ATPase activity in ex vivo samples remains unexplained.

Effects of aldosterone

The activity of Na^+,K^+-ATPase is stimulated by aldosterone, and therefore hypoaldosteronism has been implicated to cause hyperkalemia by impairing K^+ entry into cells [1, 3, 4]. However, the role of aldosterone in transcellular K^+ equilibrium remains controversial [28]. Although many studies in experimental animals and human subjects appear to demonstrate a major role for sustained changes in aldosterone in transcellular K^+ homeostasis [29–32], most have not been controlled for changes in body K^+ stores or for the effect of catecholamines [28, 31, 33]. Blockade of the normal surge in aldosterone after acute K^+ administration has no effect on the transcellular disposition of administered K^+ [34, 35]. An additional problem with positing an important effect of aldosterone on transcellular K^+ movement is that striated muscle cells, the major intracellular reservoir of K^+, lack mineralocorticoid receptors [36].

Renal regulation of K^+ homeostasis

Regardless of whether K^+ distribution in the body is normal or abnormal in patients with chronic renal insufficiency, excretion of K^+ must eventually match intake or lethal hyperkalemia will supervene within days. Potassium excretion by the kidney is tightly regulated and is determined primarily by events beyond the early distal tubule where either reabsorption or secretion of K^+ can occur [37–40]. Potassium excretion almost always exceeds the amount delivered to the early distal tubule (except under conditions of sustained K^+ depletion), indicating that the rate of secretion is the key determinant of K^+ excretion. Secretion of K^+ occurs in the collecting duct and is mediated primarily by apical membrane K^+ (ROMK) channels in the principal cells [39–41], although it may be augmented by "maxi-K" channels in the apical membrane of intercalated cells under conditions of high urine flow rates [42].

When renal function is normal, aldosterone and tubular flow rate to the distal nephron appear to be the key factors regulating K^+ excretion [43], and plasma [K^+] remains within normal levels over a wide range of dietary K^+ intake. However, as discussed below, the specific role of aldosterone remains somewhat controversial and other regulatory influences, perhaps even extracellular [K^+] itself, may play a role [44]. In adrenalectomized dogs on fixed aldosterone replacement, for example, an increase in plasma [K^+] increases urinary K^+ excretion without any change in Na^+ excretion [45]. In individuals with renal insufficiency, flow rate to the remaining functioning tubules is already maximized so that other factors must come into play to regulate K^+ excretion. We will examine the evidence that plasma [K^+] itself is a key player, which interacts with aldosterone and other factors to regulate K^+ excretion in patients with renal insufficiency.

Principal cell K^+ secretion

Potassium secretion through principal cells of the collecting duct is a two-step process involving (*1*) cellular K^+ entry across the basolateral membrane via the Na^+,K^+-ATPase pump, and (*2*) K^+ exit across the apical membrane via K^+ channels that open to allow secretion into an electronegative lumen (Fig. 3). The electronegativity of the lumen is largely due to Na^+ reabsorption through the epithelial Na^+ channel, ENaC (Fig. 4A). Potassium secretion through apical K^+ channels constitutes the rate-limiting step of K^+ secretion, and occurs through the ROMK potassium channel in the principal cells [46, 47].

Effect of hyperkalemia on K^+ secretion. The specific effects of peritubular [K^+] on distal tubular K^+ secretion and renal K^+ excretion were first elucidated in a series of in situ microperfusion studies in rats [48]. In these experiments, acute hyperkalemia was induced by intra-

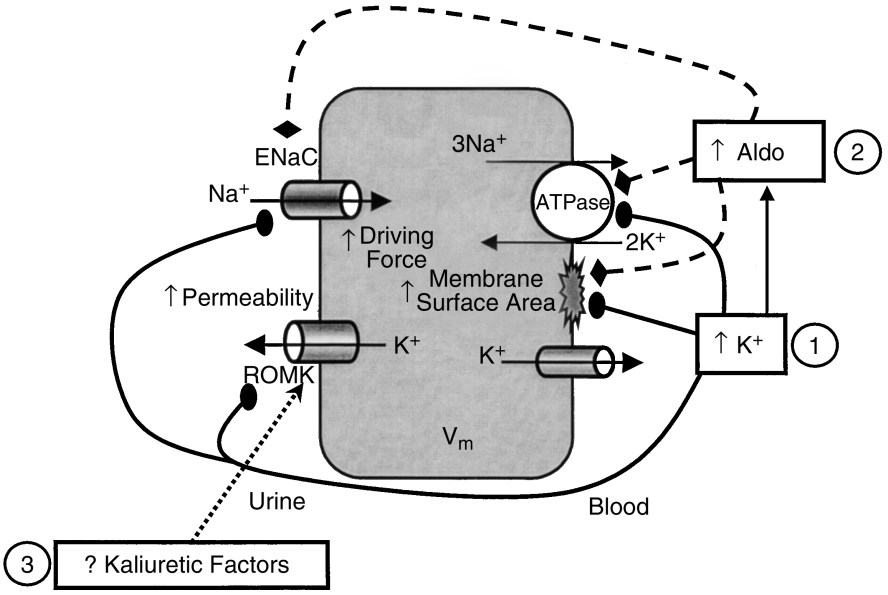

Fig. 3. Major factors that regulate K^+ secretion in principal cells. Sodium is reabsorbed across the luminal membrane through ENaC Na^+ channels, with the resultant cellular depolarization increasing the electrical driving force for K^+ secretion through ROMK K^+ channels. (*1*) Elevation of peritubular $[K^+]$ (circular arrowheads) increases the density of luminal ENaC and ROMK channels, which both promote K^+ secretion by increasing the electrical driving force and K^+ permeability, respectively. Increases in peritubular $[K^+]$ also activate the Na^+,K^+-ATPase pump in the BLM and stimulate aldosterone release. (*2*) Aldosterone (diamond arrowheads) increases the density of ENaC (but not ROMK) channels and activates the Na^+,K^+-ATPase pump, both of which increase the driving force for K^+ secretion. The surface area of the BLM containing the Na^+,K^+-ATPase pump undergoes amplification during prolonged exposure to either increased peritubular $[K^+]$ or aldosterone. (*3*) Kaliuretic factors, including K^+ itself, have been proposed that somehow directly increase K^+ secretion. For example, high luminal $[K^+]$ may directly increase the activity of ROMK channels.

venous K^+ administration into adrenalectomized rats maintained at a fixed aldosterone level. Hyperkalemia more than doubled K^+ secretion in perfused surface distal tubules and acutely increased urinary K^+ excretion. The increase in K^+ secretion induced by hyperkalemia was the same whether aldosterone secretion rate was fixed at low or high levels, indicating independence of this effect of hyperkalemia from aldosterone. Moreover, Na^+ delivery, pH, tubular flow rate, and transepithelial potential difference were all controlled, indicating a specific effect of peritubular $[K^+]$ on K^+ secretion [48].

In a related study, stimulation of distal tubular K^+ secretion by increases in plasma $[K^+]$ was shown to occur primarily when $[K^+]$ was increased from 4 to 6 mmol/L, with no further effect at higher concentrations [49]. Therefore, the effect is prompt, occurs over a range of plasma $[K^+]$ not associated with adverse events in humans, and acts in a homeostatic fashion to increase urinary K^+ excretion. Based on these studies, one can estimate that more than half of the stimulation of K^+ secretion in the distal tubule is induced by hyperkalemia, with the remainder stimulated by aldosterone [48]. In support of these results in intact rats, several studies in isolated perfused rabbit collecting ducts have shown that K^+ secretion is stimulated by an increase in peritubular $[K^+]$ [50–53].

The nature of this stimulation has been explored using electrophysiological techniques in isolated rabbit collecting tubules by Muto et al (Fig. 4) [53]. In their study, an increase in peritubular $[K^+]$ initiated the following sequence of events: (*1*) immediate activation of the Na^+,K^+-ATPase pump, (*2*) an increase in the K^+ conductance in both the apical and basolateral membranes, and (*3*) an increase in the apical Na^+ conductance. The increase in apical K^+ conductance is due to an increase in the ROMK K^+ conductance, and the increase in apical Na^+ conductance is due to an increase in the ENaC Na^+ conductance. The latter plays a key role because inhibition of ENaC by amiloride attenuates activation of the Na^+,K^+-ATPase pump, which decreases cellular K^+ entry and therefore K^+ secretion. Conversely, these effects are amplified by treatment with mineralocorticoids, which stimulates ENaC [54–56]. Careful microperfusion studies also have shown that an acute elevation of peritubular $[K^+]$ directly activates the basolateral Na^+,K^+-ATPase pump [49, 57], which secondarily increases the apical Na^+ conductance [52, 53]. Both of these changes elevate the driving force for K^+ secretion through apical ROMK channels (Fig. 4B). However, the signaling mechanisms underlying the "crosstalk" between the luminal and peritubular membranes remain unknown [58].

Interaction between K^+ and aldosterone. The interaction between extracellular $[K^+]$ and K^+ excretion involves the adrenal cortex as well as the kidney (Figs. 3 and 4). An increase in extracellular $[K^+]$ is well known to stimulate aldosterone secretion by the adrenal gland, an effect facilitated by simultaneous stimulation of angiotensin II secretion [34, 59–61]. This effect is apparent in patients with renal insufficiency as well; aldosterone correlates directly with plasma $[K^+]$ in these patients [7]. Aldosterone increases the density and activity of Na^+,K^+-ATPase pumps in the basolateral membrane (BLM) and Na^+ channels in the apical membrane [52,

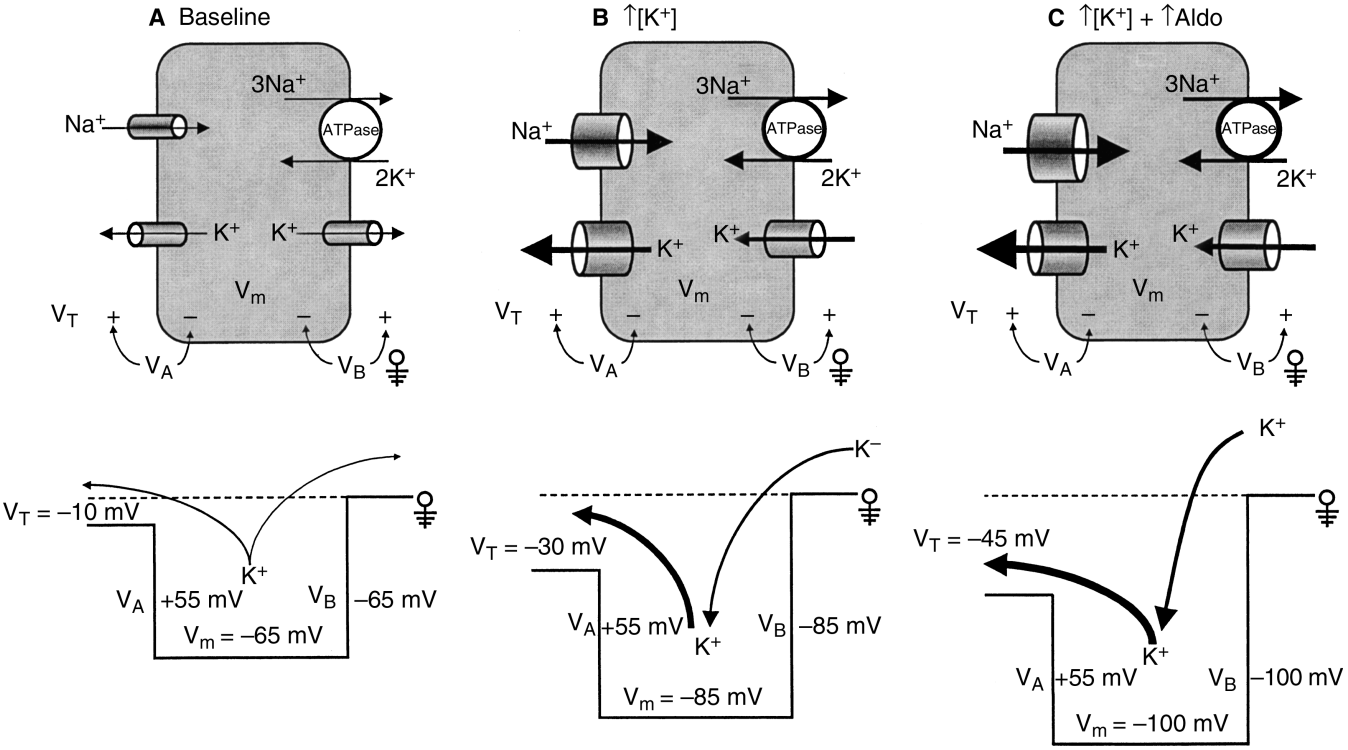

Fig. 4. Electrophysiology of K^+ secretion and K^+ adaptation in cortical collecting duct (CCD) principal cells. The luminal membrane has ENaC Na^+ channels and ROMK K^+ channels, and the peritubular membrane has K^+ channels and Na^+,K^+-ATPase pumps. The thickness of the arrow though the channels is proportional to the driving force and the size of the channel is proportional to the conductance. Stimulation of the pump is denoted by increased thickness. (*A*) At baseline, K^+ entering across the BLM via the Na^+,K^+-ATPase pump is subsequently secreted across the apical membrane into an electronegative lumen while some K^+ recycles back into the blood. (*B*) An increase in peritubular [K^+] activates the pump and leads to an increase in the K^+ conductance in the BLM, resulting in hyperpolarization of V_B. When V_B becomes more negative than E_K^{BLM}, the direction of K^+ current reverses, and K^+ enters the cell. An elevation of peritubular [K^+] also increases the density of apical membrane conductances; more Na^+ current via ENaC increases lumen electronegativity (V_T) and therefore the driving force for K^+ secretion through a higher density of ROMK channels. (*C*) The combination of increased peritubular [K^+] and mineralocorticoids further augments the changes described in panel B. Note that aldosterone leads to an increase in the driving force for K^+ secretion through ROMK channels, but does not increase the density of these channels. The **Appendix** contains a more detailed description of the electrophysiological profile under each condition. (Adapted from [56]; used with permission from the American Physiological Society).

53, 58, 62, 63], but does not increase the density of apical K^+ channels [64]. These effects of aldosterone, coupled with the increase in the density of apical K^+ channels induced by peritubular hyperkalemia, result in both an increase in K^+ permeability and driving force, which is an extremely favorable setting for K^+ secretion [54, 55, 62, 63, 65].

Additional gain is built into the system because an increase in extracellular [K^+] also stimulates aldosterone secretion, which enhances the effect of increased peritubular [K^+] on K^+ secretion. Moreover, if stimulation of secretion is prolonged, the surface area of the basolateral membrane undergoes amplification [66]. Such a chain of events explains why K^+ adaptation can be rapid [67] and robust [68]. In addition to stimulating K^+ secretion in the kidney, aldosterone stimulates K^+ secretion by the colonic epithelium, promoting stool K^+ loss [69–71]. Indirect evidence suggests that hyperkalemia also stimulates colonic K^+ secretion independent of aldosterone [69, 70].

K^+ sensors, K^+ channels, and kaliuresis. The transient hyperkalemia induced by K^+ ingestion and absorption from the gut is almost certainly the proximate signal for the acute increase in K^+ excretion by the kidney [72–75]. This renal response begins within 30 minutes of receiving a K^+ load [6, 72, 75], and probably prevents any detectable change in systemic [K^+] [73, 74]. Although aldosterone secretion also increases within minutes in response to K^+ loading [34, 75], its role in the rapid increase in K^+ excretion that follows an oral K^+ load remains controversial [47, 74, 75]. Some investigators have postulated the existence of a neuroenteric kaliuretic reflex involving a splanchnic K^+ sensor that senses dietary K^+ and somehow stimulates renal tubular K^+ secretion [74, 76]. Another possibility is that peritubular [K^+] itself is the most important kaliuretic factor.

ADAPTIVE MECHANISMS OF K^+ EXCRETION

Sustained hyperkalemia does not occur in individuals with normal renal function despite marked increases in

potassium intake, because an adaptive change in distal tubular K^+ secretion occurs such that intake is matched by rapid and equivalent increases in K^+ excretion [31, 49, 77, 78]. This response of the kidney to high dietary K^+ intake, first demonstrated in rats [79], is termed potassium adaptation. The distal tubular events induced by a high K^+ diet are identical to those observed when extracellular $[K^+]$ is increased, suggesting that such an increase may be the signal for K^+ adaptation. In experimental animals, a high K^+ diet induces an increase in ROMK channels, ENaC channels, and Na^+,K^+-ATPase pump activity, in the absence of an increase in aldosterone secretion. By contrast, when rats are given exogenous aldosterone or maintained on a low Na^+ diet to increase endogenous aldosterone levels, the density of apical ENaC channels increases, but there is no change in the number of ROMK channels [47]. Although sustained hyperkalemia does not occur when renal function is normal in experimental animals or humans ingesting a high K^+ diet, transient hyperkalemia has been observed in the postprandial period. In human subjects with normal renal function ingesting a liquid formula diet containing large amounts of K^+ (5 mmol/kg body weight) for a five-day period, serum K^+ rose transiently to between 5 and 6 mmol/L after meals (R. Tannen, personal communication). Although the factors signaling the initiation of renal K^+ adaptation remain to be defined, one factor could be a repetitive postprandial increase in extracellular $[K^+]$.

Whatever the underlying mechanisms, K^+ adaptation is characterized by changes in apical K^+ and Na^+ conductances and in basolateral Na^+,K^+-ATPase pump activity that can occur in the absence of aldosterone. In addition to an increase in plasma $[K^+]$, urinary $[K^+]$ may be part of the signaling mechanism, as a recent study has demonstrated that an elevation of luminal $[K^+]$ also increases the density of ROMK channels [80], an effect that may contribute to K^+ adaptation.

K^+ adaptation in renal insufficiency

How might hyperkalemia induce K^+ adaptation in the setting of an overall reduction in functioning nephron mass, when each remaining nephron faces an increased workload? As discussed earlier, the effects of hyperkalemia on the collecting duct are virtually identical to those seen during K^+ adaptation. They include (*1*) an amplification of basolateral membrane area [81] and Na^+,K^+-ATPase pump activity [82, 83], (*2*) an increase in apical Na^+ delivery and reabsorption [84], and (*3*) an increase in K^+ excretion per nephron in order to match K^+ intake [85]. Based on these observations, the following cascade of events may occur in renal insufficiency (Fig. 3). As ingested K^+ is absorbed and retained due an initial impairment in K^+ excretion, hyperkalemia develops, amplifying the normal signal to excrete K^+ (aldosterone and other putative kaliuretic factors). This augmented signal will lead not only to activation of the Na^+,K^+-ATPase pump and an increase in apical Na^+ channel density, but also to an increase in apical K^+ channel density [58], producing an extremely favorable milieu for K^+ secretion. Because of the decrease in functioning nephrons in renal insufficiency, the development of sustained hyperkalemia may actually be required for full K^+ adaptation in many of these patients.

HYPERKALEMIA: SIGNAL AND EFFECTS

Based on the evidence presented in this review, we propose the following scheme. Either a reduction in GFR or an increase in dietary K^+ intake causes a transient disequilibrium resulting in an increase in body K^+ stores, reflected by an increase in plasma $[K^+]$ when aldosterone or other kaliuretic factors fail to correct the imbalance. In the absence of a rapid ability to increase renal K^+ excretion and correct this disequilibrium, extracellular $[K^+]$ rises until it reaches a level sufficient to produce a sustained augmentation of renal K^+ excretion, so that excretion again matches intake. In this new steady state, plasma $[K^+]$ will remain stable at an elevated level until either dietary K^+ intake, aldosterone secretion, or renal function changes. In patients with low aldosterone levels, dietary K^+ and renal function become the primary determinants of plasma $[K^+]$. If dietary intake falls or renal function improves, plasma $[K^+]$ will fall. If intake increases or renal function deteriorates, plasma $[K^+]$ will rise until balance is again achieved.

Fragility of the new steady state

Although a new steady state may be achieved in which plasma $[K^+]$ is elevated but stable in patients with renal insufficiency, this delicate balance can easily be disrupted. It is apparent from Figure 1 that simply increasing dietary K^+ intake can raise extracellular $[K^+]$ to potentially dangerous levels. Potassium balance is more commonly disrupted by physician intervention. Indeed, the most common cause of severe hyperkalemia in patients with renal insufficiency is physician-prescribed K^+ supplements [86, 87]. In addition to K^+ itself, drugs that impair K^+ homeostasis are often responsible for disrupting the new steady state in these patients [88]. Aside from drug effects, a wide range of factors may influence transcellular K^+ distribution and exacerbate hyperkalemia in patients with decreased renal function, including metabolic acidosis, reduced β-adrenergic activity, and perhaps toxic effects on cell membrane Na^+,K^+-ATPase [4].

Therapeutic implications

Recognition that mild to moderate hyperkalemia is an adaptive response should lead to tolerance of a steady-state serum $[K^+]$ of 5.0 to 5.5 mmol/L in patients with

chronic renal insufficiency. In patients with higher serum $[K^+]$ levels, intervention should be directed at uncovering factors such as inadvertent potassium intake (for example, "salt substitutes") or drugs that impair K^+ excretion or transcellular distribution. Given the relationship shown in Figure 1, important intervention in all patients with chronic renal insufficiency and hyperkalemia should be dietary counseling to assure that foods high in K^+ content are not ingested in excessive amounts. Reduction in dietary K^+ intake to 2 to 3 g/day may even be sufficient to allow continuation of angiotensin inhibiting drugs that can prolong renal survival. Chronic Kayexalate therapy should be reserved for patients who are unable to regulate their dietary intake, and acute intervention should be reserved for those patients with extremely high serum $[K^+]$ levels (>6.5 mmol/L).

SUMMARY AND FUTURE DIRECTIONS

We propose that hyperkalemia plays a pivotal role in K^+ homeostasis. It stimulates K^+ excretion and restores balance when K^+ intake outstrips the kidney's ability to respond in patients with renal insufficiency. Hyperkalemia promotes K^+ excretion by directly stimulating K^+ secretion in collecting duct principal cells. The cellular mechanisms by which K^+ secretion is increased by hyperkalemia remain to be determined, but the effect is independent of, and additive to, the effects of aldosterone. In patients with renal insufficiency, extracellular $[K^+]$ rises to the level needed to stimulate collecting duct K^+ secretion so that renal K^+ excretion again matches intake. When this new steady state is achieved, extracellular $[K^+]$ remains stable unless dietary intake increases further, GFR falls, or drugs are given that disrupt the new balance. Management of hyperkalemia in patients with renal insufficiency should focus on preventing disruption of this new steady state by reviewing drug therapy and dietary counseling.

Our proposal that the elevation in plasma $[K^+]$ seen in many patients with chronic renal insufficiency is an adaptive signal for promoting kaliuresis and that hyperkalemia is necessary for homeostasis requires further basic and clinical investigation. For example, the physiological studies done by Muto et al on rabbits with normal renal function could be repeated using healthy tubules from animals with renal insufficiency [52, 53]. Our thesis would predict that these tubules would show an exaggerated kaliuretic response compared to those from animals with normal renal function. To examine whether the initial kaliuretic signal comes from sensing dietary K^+ or peritubular $[K^+]$, it might be possible to somehow "low $[K^+]$-clamp" one renal artery of adrenalectomized animals fed a high K^+ diet, and then compare the response of tubules from each kidney. A reasonable starting point for clinical experiments would be to place individuals with normal renal function on a high potassium diet and make frequent postprandial measurements of plasma $[K^+]$ to see whether transient hyperkalemia occurs. If so, one could then examine the relationship between dietary K^+ and the increase in renal K^+ excretion.

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APPENDIX

Refer to Figure 4. By convention, the luminal barrier voltage V_A is positive, the basolateral barrier voltage V_B is negative, and the peritubular side is ground. Therefore, the transepithelial voltage, $V_T = V_A + V_B$, is negative (that is, electronegative lumen). The Nernst potential (in mV) for K^+ across the luminal membrane is:

$$E_K^{apical} = (25.4)\ \ln([K]_{lumen}/[K]_{cell})$$

and that across the peritubular membrane is:

$$E_K^{BLM} = (25.4)\ \ln([K]_{blood}/[K]_{cell})$$

The equations for the K^+ current across each membrane are:

Apical K^+ current:

$$I_K^{Apical} = G_K^{Apical} * [(V_T - V_B) - E_K^{Apical}]$$
$$= G_K^{Apical} * [V_A - E_K^{Apical}]$$

where G_K^{Apical} is the sum of all luminal K^+ conductances.

- V_T hyperpolarizes if V_B hyperpolarizes and/or if the lumen becomes more negative (for example, with mineralocorticoid treatment and activation of ENaC).
- V_T depolarizes if V_B depolarizes and/or if the lumen becomes less negative (such as, amiloride blockade of ENaC).
- Note that since V_A is always positive and E_K^{Apical} is always negative, the apical K^+ current is always directed outward (cell → lumen):

Basolateral K^+ current:

$$I_K^{BLM} = G_K^{BLM} * [V_B - E_K^{BLM}]$$

where G_K^{BLM} is the sum of all peritubular K^+ conductances.

- K^+ current across the BLM is directed outward (cell → blood) under control conditions because V_B is less negative than E_K^{BLM}. However, high peritubular $[K^+]$ and/or treatment with mineralocorticoids lowers V_A (by increasing inward current through ENaC) and can cause V_B (and therefore V_T) to hyperpolarize (both by increasing BLM G_K and by activating the pump) more negative than E_K^{BLM}, leading to K^+ entry across the BLM (blood → cell), promoting more K^+ secretion through apical ROMK channels.

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