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Full Reviews

Integration of the response to a dietary potassium load: a paleolithic perspective

Kamel S. Kamel[1,2]*, Martin Schreiber[1] and Mitchell L. Halperin[1,2]

[1]Renal Division, St Michael's Hospital and University of Toronto, Toronto, ON, Canada and [2]Keenan Research Center in the Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, ON, Canada

*Correspondence and offprint requests to: Kamel S Kamel; E-mail: kamel.kamel@utoronto.ca

ABSTRACT

Our purpose is to integrate new insights in potassium (K^+) physiology to understand K^+ homeostasis and illustrate some of their clinical implications. Since control mechanisms that are essential for survival were likely developed in Paleolithic times, we think the physiology of K^+ homeostasis can be better revealed when viewed from what was required to avoid threats and achieve balance in Paleolithic times. Three issues will be highlighted. First, we shall consider the integrative physiology of the gastrointestinal tract and the role of lactic acid released from enterocytes following absorption of sugars (fruit and berries) to cause a shift of this K^+ load into the liver. Second, we shall discuss the integrative physiology of WNK kinases and modulation of delivery of bicarbonate to the distal nephron to switch the aldosterone response from sodium chloride retention to K^+ secretion when faced with a K^+ load. Third, we shall emphasize the role of intra-renal recycling of urea in achieving K^+ homeostasis when the diet contains protein and K^+.

Keywords: bicarbonate, intracellular potassium shift, potassium, urea recycling, WNK kinases

INTRODUCTION

Our major physiological control mechanisms were likely developed in Paleolithic times. The diet consumed by our ancient ancestors consisted mainly of fruit and berries, which provided sugar, potassium (K^+) and organic anions, but little sodium (Na^+) or chloride (Cl^-) [1]. Hence, there was a need for mechanisms to ensure renal conservation of sodium chloride (NaCl) to avoid a hemodynamic threat. Because the intake of K^+ was episodic, but large at times, to avoid the risk of dangerous hyperkalemia and cardiac arrhythmia, there was a need to have mechanisms to shift ingested K^+ rapidly into the liver before K^+ could reach the heart and mechanisms to switch the renal response from NaCl conservation to K^+ excretion.

With regard to K^+ shift into hepatocytes, we propose a novel mechanism that integrates the role of L-lactic acid released from enterocytes in the process of absorption of dietary sugars. With regard to the excretion of K^+, it is important to recognize that aldosterone can be a NaCl-retaining hormone or a kaliuretic hormone, what is known as the 'aldosterone paradox' [2]. Aldosterone causes the insertion of open epithelial Na^+ channels (ENaC) in the luminal membrane of principal cells in the cortical distal nephron (CDN), namely the late distal convoluted tubule (DCT), the connecting segment and the cortical collecting duct (CCD). This, however, could permit either NaCl retention or K^+ secretion. Thus, there must be other signals to select one of these effects. A family of organic anions that can be converted into bicarbonate ions (HCO_3^-) accompanies K^+ ingestion when its source is fruit and berries. We attempt to integrate the role of WNK kinases and modulation of delivery of HCO_3^- to the CDN to achieve the desired renal response. A different mechanism to enhance the excretion of K^+ is required if its source is from the ingestion of animal organs and hence does not come with a load of HCO_3^-. Since urea is produced from oxidation of dietary amino acids, we examine the role of intra-renal recycling of urea in this context [3].

While we admit that some of the mechanisms we propose remain speculative, we think they are plausible and hope our hypothesis will provide impetus for further investigations.

In each section, key concepts of physiology will be outlined, to set the stage for a discussion of newer findings and how

they may be integrated into the overall understanding of K^+ homeostasis from a Paleolithic perspective. Some of the clinical implications of these novel insights into K^+ physiology will be illustrated.

SHIFT OF DIETARY K^+ INTO THE LIVER

Key physiology concepts

K^+ are kept inside the cell due to the negative voltage in cell interior. To shift K^+ into cells, a more negative cell voltage is required. This is generated by increasing the flux through the sodium/potassium ATPase (Na^+-K^+-ATPase) pumps; this is an electrogenic pump which exports three Na^+ ions while importing only two K^+ ions [4]. There are three ways to acutely increase ion pumping by the Na^+-K^+-ATPase: first, a rise in the concentration of its rate-limiting substrate-intracellular Na^+; second, an increase in its affinity for Na^+ or its maximum velocity (V_{max}); third, an increase in the number of active Na^+-K^+-ATPase pump units in the cell membrane by recruitment of new units [5].

Insulin causes a shift of K^+ into cells as it promotes translocation of Na^+-K^+-ATPase from an intracellular pool to the cell membrane [6]. Insulin via atypical protein kinase C causes phosphorylation of FXYD1 (phospholemann), which increases the V_{max} of Na^+-K^+-ATPase. Insulin also activates the sodium/hydrogen exchanger-1 (NHE-1) and hence increases the electroneutral entry of Na^+ into cells [7].

Another activator of NHE-1 is a rise in intracellular H^+ concentration [8]. H^+ ions are not only a substrate for the exchanger but also increase its activity by binding to a modifier site on its intracellular domain [9]. The significance of this is described below.

Role of L-lactic acid to induce a shift of K^+ into the liver

In a recent study in fed rats and in rats with acute hyperkalemia induced by the infusion of HCl or KCl, Cheema-Dhadli *et al.* [10] have shown that the infusion of L-lactic acid was associated with a fall in the arterial plasma K^+ (P_K) due to K^+ shift into the liver. As it has previously been observed that a rise in plasma L-lactate level ($P_{L-lactate}$) in portal venous blood occurs after absorption of dietary glucose [11], these authors suggested that a possible function of this high portal venous $P_{L-lactate}$ is to prevent hyperkalemia in hepatic venous blood following the absorption of dietary K^+ from the gastrointestinal tract. It is interesting to note that the sodium-linked glucose transporter (SLGT) in this location is SLGT-1. Hence, when 1 mmol of glucose is absorbed, 2 mmol of Na^+ must be absorbed. Therefore, more ATP is required to absorb a given quantity of glucose than if the stoichiometry of the transporter was the absorption of 1 mmol of Na^+ per 1 mmol of glucose. Should glycolysis occur at a faster rate than pyruvate oxidation, L-lactic acid will be formed and released into the portal vein. The proposed mechanism by which the L-lactic acid causes a shift of K^+ into the liver is that the uptake of L-lactic acid on the monocarboxylic acid co-transporter [12] could raise the concentration of H^+ in the sub-membrane region of hepatocytes and hence activate NHE-1. The subsequent electroneutral entry of Na^+ into hepatocytes and its electrogenic exit via Na^+-K^+-ATPase will lead to a higher intracellular negative voltage and hence the retention of K^+ in hepatocytes (Figure 1). This mechanism requires the presence of insulin [10], which is released into portal venous blood in response to the sugar load from fruit and berries. The requirement for the presence of insulin may be due to its effects to cause translocation of more Na^+-K^+-ATPase units to the cell surface of hepatocytes and phosphorylation of FXYD1.

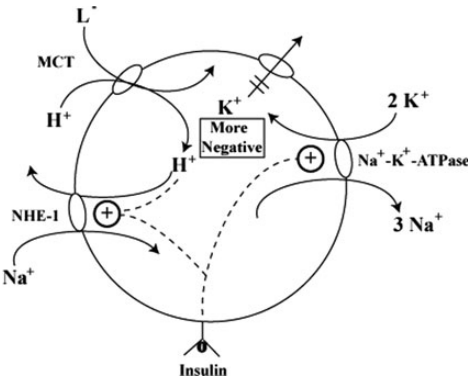

FIGURE 1: Proposed mechanism for a role of lactic acid released from enterocyte in causing a shift of K^+ into the liver. The circle represents a hepatocyte. When lactic acid enters the cell it dissociates, this may cause a large increase in the concentration of H^+ in the local sub-membrane region where NHE-1 exists. This increase in H^+ concentration can activate NHE-1 by binding to its modifier site. In the presence of insulin, which also activates NHE-1 and causes the translocation of more Na^+-K^+-ATPase subunits to the cell membrane, there will be an increase in entry of Na^+ into cells in electroneutral fashion, with its subsequent exit in electrogenic fashion. This will make the cell interior voltage more negative and result in retention of K^+ inside the cell. MCT, monocarboxylic acid transporter; L, lactate.

Clinical implications. The administration of a relatively large dose of insulin is the mainstay of therapy in patients with emergency hyperkalemia; hypoglycemia is a frequent complication. The effect of L-lactic acid to induce a shift of K^+ into the liver was also observed with the infusion of Na Lactate (unpublished observation). The administration of Na lactate with a smaller dose of insulin may provide an effective means to lower P_K with a lower risk of hypoglycemia in the emergency treatment of patients with hyperkalemia than when higher dose of insulin alone is used. Further studies are required to examine the effectiveness of this approach.

INTEGRATION OF THE RENAL RESPONSE TO DIETARY K^+ INTAKE

Control of K^+ secretion occurs primarily in the CDN [13]. Two factors influence the rate of excretion of K^+: the net secretion of K^+ by principal cells in the CDN (which raises the luminal concentration of K^+) and the flow rate in the terminal CCD [14].

K^+ secretion in CDN

Key physiology concepts. The secretory process for K^+ by principal cells in the CDN has two elements. First, a lumen-negative transepithelial voltage must be generated by electrogenic reabsorption of Na^+ (i.e. reabsorption of Na^+ without its accompanying anion, which is largely Cl^-) via the amiloride-sensitive epithelial Na channel (ENaC). Second, open renal outer medullary K^+ channels (ROMK) must be present in the luminal membrane of principal cells [15, 16].

Aldosterone actions lead to an increase in the number of open ENaC units in luminal membrane of principal cells in the CDN [17]. Aldosterone binds to its receptor in the cytoplasm of principal cells, the hormone-receptor complex enters the nucleus, leading to the synthesis of new proteins including the serum and glucocorticoid regulated kinase-1 (SGK-1) [18]. SGK-1 increases the expression of ENaC in the apical membrane of principal cells via its effect to phosphorylate and inactivate the ubiquitin ligase Nedd-4-2 [19].

In addition to transport via ENac, there are other pathways for reabsorption of NaCl in the CDN. It was thought that the paracellular pathway plays an important role in reabsorption of Cl^- in the CCD [20]. Studies by Knepper's group suggested a thiazide-sensitive, electroneutral NaCl co-transport in CCD in rats [21, 22]. Recently an electroneutral, thiazide-sensitive and amiloride-resistant NaCl transport was identified in the intercalated cells of the CCD of mice [23, 24]. This seems to be mediated by the parallel activity of the Na^+ independent Cl^-/HCO_3^- exchanger (pendrin) and the Na^+-dependent Cl^-/HCO_3^- exchanger (NDCBE) (Figure 2).

An increase in luminal fluid concentration of HCO_3^- and/or an alkaline luminal fluid pH seem to increase the amount of K^+ secreted in the CDN [25]. It was suggested that this may be due to a decrease in the paracellular permeability of Cl^- [25, 26]. A different mechanism for the effect of luminal HCO_3^- may be that since the HCO_3^- gradient is needed to increase flux through pendrin (Figure 2), an increase in luminal HCO_3^- concentration may inhibit pendrin, and hence NDCBE, and thereby the electroneutral NaCl reabsorption. In addition, there are data to suggest that an increase in luminal fluid HCO_3^- concentration increases luminal ENaC abundance and activity [27]. This may lead to a higher rate of electrogenic reabsorption of Na^+ and hence secretion of K^+, provided that open ROMK are present in the luminal membrane of principal cells.

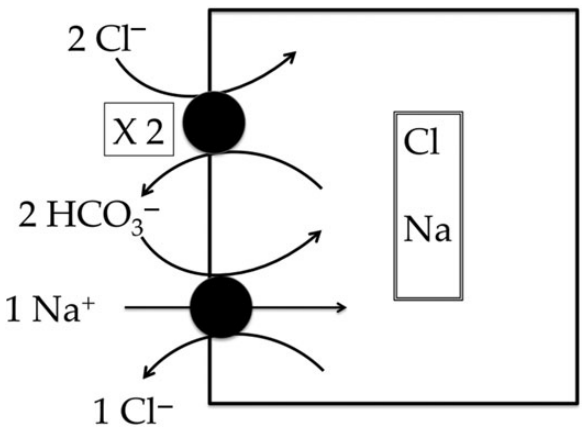

FIGURE 2: Mechanism of electroneutral NaCl transport across the luminal membrane of intercalated cells in the CCD. The top dark circle represents Pendrin. The bottom dark circle represents the Na^+-dependent Cl^-/HCO_3^- exchanger (NDCBE). The exchange of 2 Cl^- for 2 HCO_3^- via 2 cycles of pendrin with the subsequent uptake of 2 HCO_3^- and 1 Na^+ in exchange for 1 Cl^- via one cycle of NDCBE results in net electroneutral transport of 1 Na^+ and 1 Cl^- across the luminal membrane with the recycling of 2 HCO_3^- and 1 Cl^-.

Big K^+ conductance 'BK' or maxi-K^+ channels, which are activated by a rise in intracellular Ca^{2+}, are thought to play an important role in flow dependent K^+ secretion [28]. Although these channels likely mediate K^+ secretion in patients with Bartter's syndrome, which is due to a loss-of-function mutation in ROMK [29], their role in physiological regulation of renal excretion of K^+ is not clear. It is possible that BK channels may provide a way for a 'speedy' K^+ excretion if there is a large intake of K^+, if flow through CCD were augmented and if 'conductance' through ROMK in this setting is rate limiting.

Integration of the role of WNK kinases and the modulation of HCO_3^- delivery to CDN

A complex network of with-no-lysine kinases (WNKs), WNK4 and WNK1, via effects on the thiazide-sensitive NaCl cotransporter (NCC) in the DCT and on ROMK seem to function as a switch to change the aldosterone response of the kidney to either conserve Na^+ or excrete K^+, depending on whether the release of aldosterone is induced by a reduction in dietary Na^+ intake or an increase in dietary K^+ intake [30, 31]. In addition, modulation of the delivery of HCO_3^- to the CDN may play a role in determining the rate of electrogenic versus electroneutral Na^+ reabsorption as described above. The complex interplay of these mechanisms may be better understood if analyzed from a Paleolithic perspective when there was a need to both conserve NaCl as the diet was NaCl poor and therefore avoid the threat of hemodynamic instability, but also be able to excrete a large dietary K^+ load and avoid the risk of hyperkalemia.

Conservation of NaCl. WNK4 is thought to inhibit NCC activity by reducing its abundance in luminal membranes by diverting post-Golgi NCC to the lysosome for degradation [32] (Figure 3A). Angiotensin II (ANG_{II}) is released in response to low effective arterial blood volume (or low salt intake). ANG_{II} signaling through its AT1 receptor (ATR1) converts WNK4 from an NCC-inhibiting to an NCC-activating kinase. The mechanism by which ANG_{II} activates WNK4 is not clearly known but is likely to involve phosphorylation. SGK-1 also phosphorylates WNK4, and both SGK-1 and ATR1 signaling are required to switch WNK4 from an inhibitor to an activator of NCC. The activated form of WNK4 phosphorylates members of the STE20 family of serine/threonine kinases, specifically the STE 20-related proline-alanine-rich-kinase (SPAK) and the oxidative stress response kinase type 1 (OSR1). Phosphorylated SPAK/OSR1 in turn phosphorylates and activates NCC, enhancing reabsorption of Na^+ and Cl^- in DCT [33].

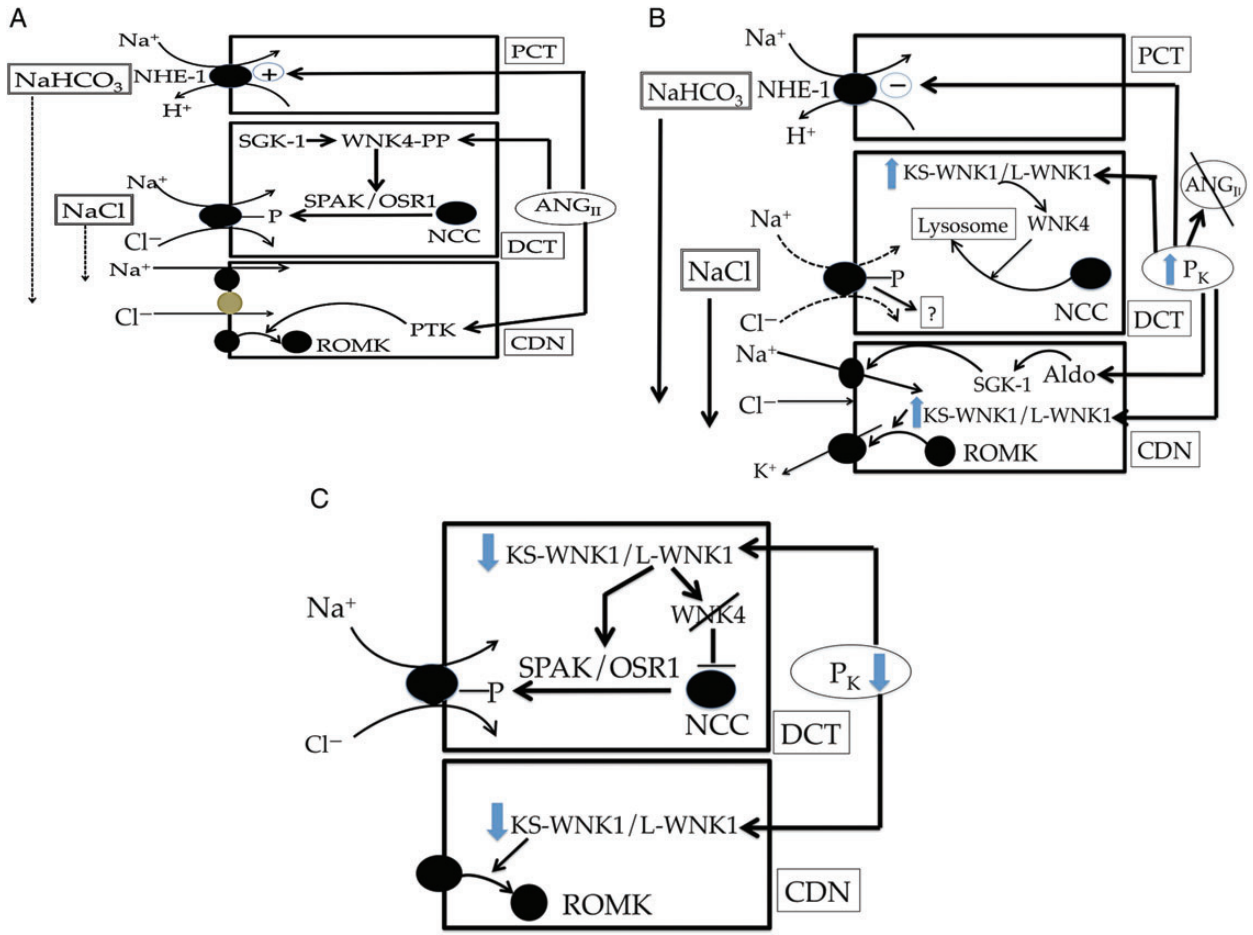

FIGURE 3: Integration of the role of WNK kinases and modulation of delivery of HCO_3^- in regulation of K^+ secretion in CDN. In (**A**) and (**B**), the upper rectangle represents a PCT cell, the middle rectangle represents a DCT cell and the lower rectangle represents a CDN cell (for illustrative purposes, we do not separate principal cells from intercalated cells). In (**C**), only a DCT cell and a CDN cell are shown. (A) The NaCl-retaining state. ANG_{II} phosphorylates and activates WNK4, activated WNK4 induces phosphorylation of SPAK and OSR1, which in turn phosphorylates and activates NCC. To prevent kaliuresis, ANG_{II} induces endocytosis of ROMK via increasing the expression of protein tyrosine kinase (PTK). ANG_{II} enhances the reabsorption of HCO_3^- in the cells of the PCT, and hence diminishes its delivery to the CDN, which will allow for electroneutral reabsorption of Na^+ by the parallel activity of pendrin and NDCBE (shown as two adjacent circles in the luminal membrane of CDN cell) and hence diminishes the luminal negative voltage. (B) The events after a K^+ load. Because of inhibition of ANG_{II} release, and an increase in the ratio of KS-WNK1 to L-WNK1, WNK4 will be in its NCC-inhibiting mode. Existing phosphorylated NCC in luminal membrane will need to be de-activated or removed from the luminal membrane to allow for more NaCl to be delivered downstream. The increase ratio of KS-WNK1 to L-WNK1 leads to more ROMK units in the luminal membrane of principal cells in CDN. A higher P_K leads to inhibition of the reabsorption of HCO_3^- in the PCT. A higher luminal HCO_3^- concentration increases the rate of electrogenic reabsorption of Na^+ and the generation of luminal negative voltage. (C) Events involved in re-establishment of the NaCl-retaining mode. As the ratio of KS-WNK1 to L-WNK1 isoforms is reduced, L-WNK1 exerts its effects to up-regulate NCC either by blocking the inhibitory form of WNK4 or directly by phosphorylation of SPAK/OSR1. L-WNK1 also inhibits ROMK via endocytosis. As ANG_{II} is released, WNK4 will be converted to its NCC-activating kinase form. The effects of ANG_{II} to diminish the delivery of HCO_3^- to the CDN and to inhibit ROMK will reestablish the role of aldosterone as a NaCl-retaining hormone in CDN.

This effect of ANG_{II} diminishes the delivery of NaCl to the CDN; ANG_{II}, however also causes the release of aldosterone and SGK-1. This would tend to enhance K^+ excretion; therefore, other mechanisms are needed to make aldosterone function in CDN as a NaCl-retaining hormone and not a kaliuretic hormone. First, ANG_{II} has been shown to inhibit ROMK activity in dietary K^+-restricted rats, but not in rats on their usual dietary K^+ intake [34]. The effect of ANG_{II} may be mediated via increasing the expression of protein tyrosine kinase such as c-Src, which phosphorylates ROMK and results in its endocytosis, so that it is not available to permit secretion of K^+ [35]. Second, ANG_{II} is a potent activator of sodium/hydrogen exchanger-3 (NHE-3) and the reabsorption of HCO_3^- in the cells of the PCT [36]. Therefore, there will be diminished delivery of HCO_3^- to the CDN, which may allow for more electroneutral than electrogenic reabsorption of Na^+ in this nephron segment and hence more NaCl retention and less kaliuresis (Figure 3A) [2].

Excretion of a large K^+ load. In response to a large intake of K^+, the release of ANG_{II} is inhibited while the release of aldosterone and SGK-1 is stimulated. Increasing K^+ secretion

requires the delivery of more NaCl to CDN by inhibiting its reabsorption in DCT. In the absence of sufficient ANG_{II}, WNK4 will be in its NCC-inhibiting form because of the dual requirement of both SGK-1 and ATR1 signaling to activate WNK4. Alternative promoter usage of the WNK1 gene produces a kidney-specific, truncated form of WNK1, called KS-WNK1, and a more ubiquitous long form, called L-WNK1 [34]. L-WNK1 imposes an inhibitory effect on WNK4 [35]. The KS-WNK1 isoform blocks this effect of L-WNK1 on WNK4 (Figure 3B). An increase in dietary K^+ leads to an increased ratio of KS-WNK1 to L-WNK1, hence WNK4 will be in its NCC inhibiting mode. WNK4, however, does not cause endocytic retrieval of NCC, but rather interferes with the forward trafficking pathway by diverting NCC to the lysosome for degradation and hence reduces its steady state abundance in the luminal membrane in the DCT. Studies by Vallon *et al.* [37] showed decreased renal expression of total and phosphorylated NCC in mice on a high K^+ diet. A mechanism is needed, however, to de-activate the existing NCC units in the luminal membrane (perhaps via de-phosphorylation) or cause their removal from the luminal membrane in response to an acute K^+ load. The mechanism involved and how it is regulated are yet to be identified.

Nevertheless, as delivery of NaCl to the CDN is increased, two additional requirements are needed to achieve a high rate of K^+ secretion in the CDN: a high rate of electrogenic reabsorption of Na^+ and open ROMK in the luminal membrane of principal cells. In Paleolithic times, the major source of dietary K^+ was from fruit and berries, with organic anions that are metabolized to HCO_3^-. This increases the filtered load of HCO_3^-. In addition, a higher P_K is associated with alkalinization in PCT cells, which leads to inhibition of the reabsorption of HCO_3^- and an increase in its distal delivery [38]. An increase in luminal HCO_3^- concentration may increase the rate of electrogenic reabsorption of Na^+. For this, however, to result in kaliuresis, ROMK channels in an open configuration must be present in the luminal membrane of principal cells. Two processes seem to be involved. First, WNK4 inhibits ROMK by stimulating endocytosis of the channel via clathrin-coated vesicles [39]. When ANG_{II} is suppressed but SGK-1 is present (as in conditions of high K^+ intake), SGK-1 phosphorylates WNK4 and reverses its inhibition of ROMK [40]. Second, L-WNK1 inhibits ROMK by inducing its endocytosis; the KS-WNK1 isoform inhibits this effect of L-WNK1. The relative abundance of the WNK1 isoforms is regulated by dietary K^+. An increase in dietary K^+ leads to an increased ratio of KS-WNK1 to L-WNK1, so there is reduced endocytosis of ROMK; the ratio is decreased by dietary K^+ restriction, which thereby leads to greater endocytosis of ROMK [40].

Re-establishment of a NaCl-retaining state. As the danger of a large K^+ load is dealt with, the NaCl-retaining mode needs to be re-established. L-WNK1 up-regulates NCC either by blocking the inhibitory form of WNK4 or directly by phosphorylation of SPAK/OSR1, and hence enhances the reabsorption of NaCl in DCT [41] (Figure 3C). A reduction in the ratio of KS-WNK1 to L-WNK1 transcripts leads to greater endocytosis of ROMK [42]. As ANG_{II} is released, WNK4 will be converted to its NCC-activating kinase form. The effects of ANG_{II} to diminish the delivery of HCO_3^- to the CDN (which increases electroneutral reabsorption of Na^+) and to inhibit ROMK will reestablish the role of aldosterone as a NaCl-retaining hormone in CDN.

Clinical Implications

Familial hyperkalemia with hypertension. Patients with this syndrome (also known as Pseudohypoaldosteronism type II or Gordon's syndrome) behave as if they have a gain-of-function in the thiazide-sensitive NCC. Major deletions in the genes encoding for WNK1 and missense mutations in WNK4 have been reported in these patients [43]. Hypertension and hyperkalemia in these patients respond nicely to thiazide diuretics, which may reflect their effect to inhibit NCC but also the electroneutral reabsorption of Na^+ in CCD.

Syndrome of hyporeninemic hypoaldosteronism. A similar set of clinical findings to those patients with 'Familial Hyperkalemia with Hypertension' may occur in other patients, most commonly those with diabetic nephropathy [44]. Support for the hypothesis that suppression of renin release is the result of volume expansion is the finding that circulating atrial natriuretic peptide blood levels are elevated in these patients [45], and many will respond to either NaCl restriction or furosemide with an increased plasma renin mass [45]. It is possible that the reabsorption of Na^+ and Cl^- in these patients may be augmented in the DCT. Of relevance to patients with type 2 diabetes mellitus, who often have hyperinsulinemia and the metabolic syndrome, it has been noted that chronic insulin infusion in rats is associated with the retention of NaCl due to its enhanced reabsorption in different nephron segments including the DCT. There is also less WNK4 expression in the renal cortex [46]. Furthermore, obese Zuker rats were shown to be more sensitive to thiazides than their lean counterparts with a greater natriuresis, kaliuresis and drop in blood pressure [47]. Reduced renal cortical expression of WNK4 was also observed in this model. In addition, work in cell culture indicates involvement of PI3-kinase in activating WNK1 [48]. Thiazide diuretics may be particularly effective in these patients.

Hyperkalemia with calcineurin inhibitors. Hoorn *et al.* [49] demonstrated that tacrolimus caused salt-sensitive hypertension and increased the abundance of phosphorylated NCC and the NCC-regulatory kinases WNK3, WNK4 and SPAK in mice. Hydrochlorothiazide reversed tacrolimus-induced hypertension. Tacrolimus treated mice developed hyperkalemia when they consumed a high K^+ chow.

Increasing K^+ secretion with induction of bicarbonaturia. Inducing bicarbonaturia with the administration of acetazolamide, a carbonic anhydrase inhibitor, may increase the excretion of K^+. This may be an option for treatment of patients with mild-to-moderate hyperkalemia due to the use of renin-angiotensin-aldosterone blockers, which might allow the continuation of these medications. To prevent the development of metabolic acidosis, administration of $NaHCO_3$ may be required. This needs to be examined in a clinical study.

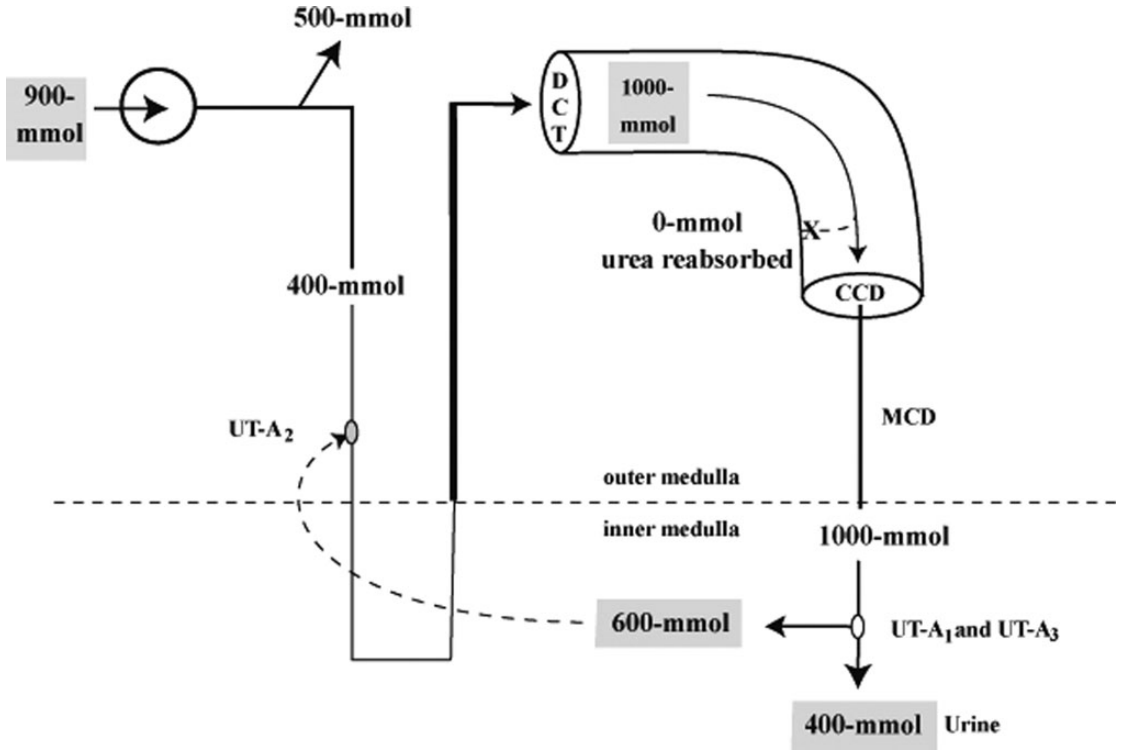

FIGURE 4: Intra-renal recycling of urea. Vasopressin phosphorylates and causes the insertion of urea transporters (UT) UT-A1 and UT-A3 in the luminal membrane of cells in the inner medullary collecting duct (MCD) [51]. A higher concentration of urea in the luminal fluid in the inner MCD than that in the interstitial fluid in the inner medulla is achieved because all the segments of the late distal nephron upstream to the inner MCD are likely to be impermeable to urea, but permeable to water owing to the insertion of AQP2 into the luminal membranes of principal cells. The bulk of the urea that is reabsorbed in the inner MCD leaves the inner medulla via ascending vasa recta, because it has UT-A2. Most of this urea will enter the luminal fluid of the descending thin limbs (DtL) of the loop of Henle of superficial nephrons that have their bends deep in the outer medulla, as they possess the UT-A2 and the concentration of urea is higher in the interstitial compartment than in the luminal fluid of the DtL, which allows for a high rate of delivery of urea to the early DCT [52]. This calculation does not take into account the relatively small amount of urea that exits the medulla via the ascending vasa recta.

Flow rate in the CCD

Key physiology concepts. When vasopressin acts, the late distal nephron is permeable to water owing to the insertion of aquaporin-2 water channels (AQP2) in the luminal membrane of principal cells. The osmolality of fluid in the terminal CCD becomes equal to the plasma osmolality and hence is relatively fixed. Therefore, the number of osmoles present in luminal fluid determines the flow rate in the terminal CCD [14]. These osmoles are largely urea, Na^+, Cl^- and K^+ with an accompanying anion.

Intra-renal recycling of urea. This process is illustrated in Figure 4. To obtain a quantitative estimate of the amount of urea that is recycled, one needs an estimate of the amount of urea that is delivered to the early DCT. Using data from micropuncture studies in fed rats, the amount of urea in the early DCT was 1.1 times the amount of urea that was filtered [50]. Extrapolated to an adult human with a GFR of 180 L/day, and a plasma urea concentration of 5 mmol/L, a reasonable estimate of the daily delivery of urea to the early DCT is ~1000 mmol/day. Since subjects eating a typical Western diet excrete close to 400 mmol of urea per day, the amount of urea that recycles would be ~600 mmol per day. This process of urea recycling adds an extra 2 L to the flow rate in terminal CCD (600 mosmol divided by a luminal fluid osmolality that is equal to plasma osmolality, i.e. ~300 mOsm/L).

Integration of intra-renal recycling of urea into renal K^+ excretion

The importance of this process of intra-renal recycling of urea for K^+ excretion becomes evident when one considers that the second source of dietary K^+ is from ingestion of animal organs (e.g. muscle). The anions that accompany this K^+ load are organic phosphates or sulfate, which unlike HCO_3^-, do not augment the secretion of K^+ in the CDN, unless the concentration of Cl^- in luminal fluid in the CDN is very low [53]. At the same time, urea is produced when the amino acid constituents of protein are oxidized [54]. By increasing the volume of fluid that exits the terminal CCD, this process of urea recycling aids the excretion of a K^+ load from the ingestion of dietary proteins [55].

Clinical implications. In a quantitative analysis, Kamel and Halperin illustrated that even in patients with a large defect in their ability to generate a lumen negative voltage in CDN, a significant degree of hyperkalemia is not likely to develop,

while consuming a usual K^+ intake, unless there is decreased flow rate in terminal CCD [55]. Since, owing to the process of intra-renal urea recycling, a large fraction of the osmoles delivered to terminal CCD are urea, restricting protein intake may decrease the amount of urea that recycles and hence the rate of flow in terminal CCD. This analysis may provide new insights into the pathophysiology of hyperkalemia that may develop in some patients on an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. It is interesting to note that ANG_{II} stimulates the transport of urea in the inner MCD in the presence of vasopressin [56]. Hence, hyperkalemia may be more likely to develop in patients who are taking these drugs if they are protein restricted, since there would now be two reasons for diminished urea recycling and therefore diminished flow in terminal CCD.

SUMMARY

In summary, our purpose was to integrate new insights in K^+ physiology into an understanding of K^+ homeostasis, viewed from a Paleolithic perspective. The release of L-lactic acid into portal venous blood in response to ingestion of fruit and berries and its entry into hepatocyte may cause an increase in H^+ concentration near NHE-1, and in the presence of insulin, induce a shift of K^+ into hepatocyte and hence prevent a dangerous rise in P_K in blood reaching the heart. In response to a large intake of K^+, because of the inhibition of the release of ANG_{II} and the increase in KS-WNK1 to L-WNK1 ratio, WNK4 will be in its NCC-inhibiting mode. A mechanism is needed to de-activate the existing NCC units in the luminal membrane or cause their removal to increase the delivery of NaCl to CDN. Increasing delivery of HCO_3^- to CDN increases the rate of electrogenic reabsorption of Na^+ in CCD, which promotes kaliuresis. An increase in ratio of KS-WNK1 to L-WNK1 isoforms causes more ROMK to be present in luminal membrane of principal cells. The process of urea recycling, by increasing the volume of fluid that exits the terminal CCD, aids the excretion of a K^+ load from the ingestion of dietary protein. Some of the clinical implications of these new insights were illustrated.

CONFLICT OF INTEREST STATEMENT

None declared.

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