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Interacting influence of diuretics and diet on BK channel-regulated K homeostasis

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Abstract

Large conductance, Ca-activated K channels are abundantly located in cells of vasculature, glomerulus and distal nephron, where they are involved in maintaining blood volume, blood pressure and K homeostasis. In mesangial cells and smooth muscle cells of vessels, the BK- α pore associates with BK- β 1 subunits and regulates contraction in a Ca-mediated feedback manner. The BK- β 1 also resides in connecting tubule cells of the nephron. BK- β 1 knockout mice (β 1KO) exhibit fluid retention, hypertension, and compromised K handling. The BK- α / β 4 resides in acid/base transporting intercalated cells (IC) of the distal nephron, where they mediate K secretion in mammals on a high K, alkaline diet. BK- α expression in IC is increased by a high K diet via aldosterone. The BK- β 4 subunit and alkaline urine are necessary for the luminal expression and function of BK- α in mouse IC. In distal nephron cells, membrane BK- α expression is inhibited by WNK4 in *in vitro* expression systems, indicating a role in the hyperkalemic phenotype in patients with familial hyperkalemic hypertension type 2 (FHHT2). β 1KO and BK- β 4 knockout mice (β 4KO) are hypertensive because of exaggerated ENaC-mediated Na retention in an effort to secrete K via only ROMK. BK hypertension is resistant to thiazides and furosemide, and would be more amenable to ENaC and aldosterone inhibiting drugs. Activators of BK- α / β 1 or BK- α / β 4 might be effective blood pressure lowering agents for a subset of hypertensive patients. Inhibitors of renal BK would effectively spare K in patients with Bartter Syndrome, a renal K wasting disease.

Introduction

Large conductance, Ca-activated K channels (BK), are localized in a variety of kidney cells, where they have far-ranging roles from regulators of glomerular filtration to conduits for potassium secretion. Previous reviews have summarized the topic of BK as a K secretory channel [1-4]. This review will emphasize studies of BK in the kidney with respect to diuretics, diet and pathological conditions. Our understanding of BK-mediated K secretion has advanced markedly in recent years due to studies with genetically altered mice. For several years, the renal outer medullary K channel (ROMK) has been the most extensively studied K secretory channel because of its localization in principal cells of the cortical collecting duct and its high open probability at resting membrane potentials. However, either

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ROMK or BK may be the predominating K secretory channel, depending on the dietary conditions [1].

Because plasma [K] must be regulated within very narrow limits, it is not surprising that redundancies for eliminating K have evolved. Either ROMK or BK knockout mice exhibit minimal problems and maintain K homeostasis when consuming a normal K diet. However renal responsiveness to consuming a high K, alkaline diet is seriously impaired in BK- β 4 knockout mice (β 4KO) and their plasma [K] increases markedly. Therefore, BK is probably the “ancient” channel, shown to secrete K in the mammalian gastrointestinal tract [5], amphibian kidneys [6], and in mammals on a high K, alkaline diet [7].

Several studies have shown the health benefits of the “Mediterranean” or “Paleolithic” diet, which consists of fruits and vegetables and is alkaline [8-10]. It is important to determine how K is handled with the ancient diet and determine whether the old standards for diuretic therapy and K homeostasis still apply. The increasing number of individuals now on ancient diets may experience dangerous elevations in plasma [K] levels when given the most popular diuretic agents that normally reduce plasma [K] of those on the “Western” acidic diets.

Localization of BK in the kidney

All smooth muscle cells, including those of the renal vessels [11-13], contain BK. Because of inaccessibility to patch clamping, BK have been difficult to identify and study *in vivo* or in isolated glomerular cells. However, BK have been studied in detail in cultured podocytes [14] and mesangial cells [15;16], where they are abundantly expressed.

Before BK were immunologically identified in specific renal segments, they were identified at the apical membrane of rabbit and rat cortical collecting ducts (CCD) using patch clamping [17;18]. Perfusion of isolated collecting ducts revealed that iberiotoxin, a specific pharmacological blocker of BK, could inhibit K secretion during high tubular fluid flows [19].

The pore-forming BK- α was found most abundantly within the acid/base transporting intercalated cells (IC) of the CNT and collecting duct by both patch clamping [20] and immunohistochemical staining (IHC) [21] (see figure 1). In the medullary collecting duct (MCD), BK- α appears mostly peri-nuclear in PC and IC [21].

In all cells where BK is expressed, one of four beta subunits (BK- β 1-4) is associated with the pore-forming BK- α . The different BK subunits modify the BK- α properties in different ways. Three of the four BK subunits (BK- β 1, β 2, and β 4) have been identified by Western blot of mouse kidney [22] and RT-PCR of isolated rat CCDs [23]. IHC subsequently localized the BK- β 1 to the apical membrane of the mouse CNT and the CNT and initial CCD of the rabbit [24]. IHC has yet to identify the localization of BK- β 3. IC *in vivo* [22;25] and the IC cell line, MDCK-C11, exhibit an abundance of BK- α and BK- β 4 by RT-PCR, Western blot and IHC [26].

Regulation of BK in the kidney

Two major kinase systems, the aldosterone-induced serum and glucocorticoid kinase (SGK) system, which regulates the ENaC-mediated Na reabsorption in exchange for either K or H secretion, and the with no lysine kinase (WNK) system, which regulates NKCC and NCC in the thick ascending limb and early distal tubule, have emerged as two primary signaling networks governing Na and K homeostasis in the kidneys.

Aldosterone

A high K diet increases plasma [K], which stimulates the production of aldosterone, yielding increased total cellular, but not surface, BK- α expression in the kidney [21;27]. Aldosterone similarly increases BK- α expression in the colon [28]. An alkaline luminal fluid enhances expression of BK- β 4, which promotes apical localization of BK- α in IC, possibly by inhibiting its degradation through the lysosomal pathway [21]. At the same time, aldosterone also enhances the driving force for K secretion by increasing ENaC and Na-K-ATPase-mediated Na reabsorption in PC [29;30] (see Figs 1 and 2).

WNK4-SPAK system

Aldosterone can be secreted from the adrenal glomerulosa in response to high plasma [K] or to low Na intake that activates the renin-angiotensin II (ANGII) axis. The low Na axis results in increased NCC-mediated Na reabsorption in the DCT and the high plasma [K] axis increases ROMK-mediated K secretion in exchange for ENaC-mediated Na reabsorption in the CNT and initial cortical collecting duct. The difference between the two actions of aldosterone is the compounded effects of high ANGI, in the case of low Na axis, which acts through a WNK4-SPAK kinase system, to promote the incorporation of NCC into the luminal membrane [31-33].

A common mutation of WNK4 renders exaggerated Na and Cl reabsorption and K retention, a disease known as familial hyperkalemic hypertension (FHHt) [34]. The hyperkalemia of FHHt indicates that WNK4 may also directly inhibit K channel mediated K secretion in the CNT and CCD. Expressing BK- α in HEK-293 cells showed that WNK4 inhibits BK activity by enhancing its ubiquitination and degradation [35] or via the MAPK pathway [36], which inhibits BK expression in the principal cells of the rat cortical collecting duct [35]. Zhuang *et al* also showed that WNK4 led to the degradation of BK- α in HEK-293 cells through the lysosomal pathway [37].

A variety of other signaling networks seem to converge on BK in the CCD; however the relevance is still uncertain in most cases. Urinary carbon monoxide activates BK in the CCD through a nitric oxide-cGMP-independent pathway [38]. Nitric oxide stimulates, while reactive oxygen species inhibits BK in the renal artery [12]. Epoxyeicosatrienoic acid (EET) activates [39] BK in the CCD and prostaglandin E2 (PGE2) inhibits BK in the CCD through the MAPK pathway [40]. Protein kinases A and C may also regulate BK in the CCD [41].

BK in hypertension and disease

Knockouts of the BK- β 1 subunit (β 1KO) are hypertensive [42-45] and exhibit cardiac hypertrophy when consuming a high K diet for only 7-10 days [2]. The BK- β 1 associates with the BK- α in all smooth muscle cells, where it increases the sensitivity of the BK- α to Ca, an effect that increases its action as a feedback regulator of contraction. The absence of BK- β 1 diminishes coupling of BK to Ca sparks, which enhances vessel tone [46] and results in an elevation of mean arterial pressure (MAP) by about 15 mm Hg above normal. Although BK are localized in renal vessels, results indicate that these BK do not play a significant role as feedback regulators of renal blood flow in response to angiotensin II, norepinephrine or vasopressin [13;47]. Therefore, β 1KO hypertension is partly due to a global increase in blood vessel tone and not the result of impaired regulation of renal blood flow.

Further analysis of mice renal function using metabolic cages revealed that the hypertension of β 1KO was exacerbated by a high K diet and was the result of fluid accumulation and aldosteronism due to the failure to eliminate K [44]. The hypertension of β 1KO on a high K diet was very responsive to eplerenone, which inhibits aldosterone receptors [44]. On a high

K diet, the fluid retention was completely eliminated by eplerenone, but significant hypertension of about 8 mmHg remained, indicating a combination of vascular tone and fluid accumulation effects.

Knockouts of the BK- β 4 subunit (β 4KO) also exhibit fluid retention and hypertension on a high K diet; however, the hypertension is milder than that of β 1KO, probably because the vascular component is not involved in the hypertension [2]. The results of these studies highlight the hypertensive consequences of the failure to eliminate K appropriately when consuming a high K diet.

The hypertension described for BK- α knockouts, BK- α -KO, β 1KO and β 4KO is mild and probably would only be obvious in humans on a high K diet. A population of BK mutations on a high K diet would be difficult to detect. However, there are reports of hypertensive patients who have aldosteronism and are resistant to all diuretic therapy except for aldosterone receptor blockers [48], which would attenuate the Na retention by ENaC that is attempting to compensate for the failure of BK-mediated K secretion by the less efficient Na for K exchange in PC. Several studies have revealed an association between single nucleotide polymorphisms (SNPs) in BK- β 1 and hypertension [49-51]. It would be interesting to determine whether a population of hypertensive individuals (with high plasma [K] and aldosteronism) has specific mutations in BK- β 1.

BK-mediated K excretion with diuretics and salt-wasting disorders

The relevance of the BK- α/β 4 is best demonstrated by animals placed on a low Na, high K, alkaline diet (LNaHK-alk), which mimics the diet of ancient man and the present-day Yanomami of South America [52]. On a normal diet, Na is reabsorbed via ENaC in exchange for K secretion via ROMK in the PC without requiring alkalinity to maintain normal plasma K. However, when dietary Na is very low and the K is high, the exchange requires alkalinity and the BK- α/β 4 to eliminate the K (D Wen *et al.*, unpublished). In β 4KO mice, compared with wild type (WT), on a low Na, high K, alkaline diet, the capacity to secrete K is diminished considerably, while the ability to reabsorb Na is intact or enhanced. However, the high capacity of WT to secrete K on LNaHK is still linked to ENaC-mediated Na reabsorption. Therefore, BK- α/β 4 has a role to enhance the coupling of K secreted per Na reabsorbed when given the LNaHK, alkaline diet. Except for the fact that both pendrin-mediated HCO₃ secretion and BK- α/β 4-mediated K secretion are located on the apical membrane of IC, the mechanism is not understood.

A high K diet enhances urinary flow in mice by more than 5-fold [7]. High flow increases BK- α/β 4 channel activity in IC, partially by releasing urine ATP [53;54]. The increased luminal volume dilutes the K in the CCD in order to maintain a chemical secretory gradient. Flow is increased by K recycling, which ensures a high medullary K concentration that inhibits Na reabsorption in the thick ascending limb [55].

The natural mechanism to eliminate K by high flow is mimicked by blood pressure lowering agents, such as furosemide and hydrochlorothiazide, which inhibit Na reabsorption by NKCC of the thick ascending limb and the NCC of the early distal tubule, respectively. As expected, a complicating side effect of such diuretics is kaliuresis and hypokalemia due to the increased volume to the aldosterone sensitive distal nephron (ASDN). Moreover, the loss of Na and body fluids increases aldosterone, which enhances expression of ENaC and Na-K-ATPase, increasing Na for K exchange.

Potassium is often supplemented with diuretics in order to prevent hypokalemia. However, the dogma of K loss with a diuretic would not apply for some popular vegetarian diets, which are low in Na, high in K and alkaline. Thiazides will be less effective diuretics

because the NCC-mediated Na reabsorption is overshadowed by ENaC-mediated Na reabsorption in order to eliminate K. Moreover, a high K intake may turn off WNK4-regulated NCC in favor of ENaC-mediated Na for K exchange [56]. More severe problems could occur with furosemide. Animals on a high K diet may utilize the NKCC1 on the basolateral membrane of the collecting duct IC to extrude K [57]. Thus, furosemide could cause hyperkalemia in patients on an ancient diet instead of the usual hypokalemic response afforded to patients on an acidic, high Na diet.

Two genetic disorders, Bartter Syndrome, a defect of Na reabsorption in the thick ascending limb, and Gitelman Syndrome, a defect of Na reabsorption by the NCC of the early distal tubule, are often associated with severe K wasting because of high volumes delivered to the aldosterone-sensitive distal nephron that stimulate BK-mediated K secretion. Bartter and Gitelman syndromes are the genetic equivalents to administering furosemide and thiazides, respectively. For these conditions, a specific inhibitor of renal BK- α/β_4 should prevent K wasting. However, BK inhibitors such as paxilline and Iberiotoxin would have profound global effects on all BK channels.

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Highlights

- BK are expressed in the cells of vasculature, glomerulus, and distal nephron.
- BK mediate K secretion when consuming a low Na, high K, alkaline diet.
- BK are regulated by aldosterone/SGK and WNK4/SPAK pathways in the kidney.
- BK deficiency is related to hypertension.
- Results of diuretic therapy are altered by BK-mediated K secretion.

Figure 1.

IHC of BK- α in cortical collecting ducts revealing cytosolic vs apical expression in WT and β 4KO on control, HK-alk and HK-Cl diet. BK- α resides in the apical membrane only in WT on HK-alk diet.

Figure 2. Regulation of BK-α/β4 in kidney

Urinary pH regulates BK-β4 expression. Plasma aldosterone (Aldo) binds to the mineralocorticoid receptor (MR), which increases BK-α transcription and expression. BK-β4 stabilizes BK-α expression at the apical membrane of IC by inhibiting the degradation via lysosomal/proteosomal pathway, while WNK4/SPAK kinase system promotes it.