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Role of BK channels in hypertension and potassium secretion

J. David Holtzclaw¹, P. Richard Grimm², and Steven C. Sansom¹

¹Department of Cellular and Integrative Physiology, University of Nebraska Medical Center; Omaha, NE

²Department of Physiology, University of Maryland School of Medicine, Baltimore, Maryland, USA

Abstract

Purpose of review—To summarize recent studies of hypertension associated with a defect in renal K excretion due to genetic deletions of various components of the large, Ca-activated K channel (BK), and review new evidence and theories regarding K secretory roles of BK in intercalated cells.

Recent Findings—Isolated perfused tubule methods have revealed the importance of BK in flow-induced K secretion. Subsequently, mice with genetically deleted BK subunits revealed the complexities of BK-mediated K secretion. Deletion of the BK α results in extreme aldosteronism, hypertension and an absence of flow-induced K secretion. Deletion of the BK β 1 ancillary subunit results in decreased handling of a K load, increased plasma K, mild aldosteronism and hypertension that is exacerbated by a high K diet. Deletion of the BK β 4 (β 4KO) leads to insufficient K handling, high plasma K, fluid retention, but with milder hypertension. Fluid retention in β 4KO may be the result of insufficient flow-induced secretion of ATP, which normally inhibits epithelial Na channels (ENaC).

Summary—Classical physiological analysis of electrolyte handling in knock-out mice has enlightened our understanding of the mechanism of handling K loads by renal K channels. Studies have focused on the different roles of the BK- α 1 and BK- α 4 in the kidney. BK α 1 hypertension may be a “three-hit” hypertension, involving a K secretory defect, elevated production of aldosterone, and increased vascular tone. The disorders observed in BK knock-out mice have shed new insights on the importance of proper renal K handling for maintaining volume balance and blood pressure.

Keywords

potassium; cortical collecting duct; BK channels; intercalated cells; aldosterone

Introduction

Potassium secretion is regulated in the distal nephron by at least two types of channels: ROMK (Kcnj1; Kir1.1), which is responsible for basal levels of K secretion, and BK. Several laboratories have studied ROMK and its regulation by a variety of signaling pathways [1–4]. Mice respond to aldosterone and a high K diet with increased ROMK expression in luminal membranes of the CCD [5;6]. BK knock-out mice (BK KO) exhibit profound aldosteronism but are able to excrete K via compensatory increases in ROMK [7].

Corresponding author: Steven C. Sansom, Dept. of Cellular and Integrative Physiology, 985850 Nebraska Medical Center, Omaha, NE 68198-5850, (402) 559-2919, (402) 559-4438 (Fax), ssansom@unmc.edu.

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However, ROMK knock-outs exhibit normal plasma [K] [8] due to aldosteronism and reduced Na and Cl reabsorption in the thick ascending limb with enhanced distal flow.

BK is normally associated with one of four subunits (BK 1- 4) and is responsible for flow-induced K secretion [9–13]. Other tissues that actively secrete K, such as the submandibular gland [14], pancreas [15] and distal colon [16;17], seem to rely only on BK. Although BK was the first K-selective channels described in the distal nephron [18], its role in K secretion has been elucidated more recently as reported in other reviews of this topic [19–24]. Other renal K channels, besides ROMK and BK, may secrete K [25;26]; however, their roles are not yet defined.

It has been known for several years that flow enhances K secretion [27–30]. The relevance of flow-induced K secretion relates to consuming a high K diet, which elevates plasma [K] and stimulates the production of aldosterone, which enhances the driving force for K secretion. Potassium secretion continues until the transtubular electrochemical gradient reverses and favors K reabsorption [31]. At this point, the [K] increases in the medullary interstitium to levels that inhibit Na and Cl transport in the thick ascending limb [32], thereby increasing flow like a natural loop diuretic. The increased tubular volume [33] maintains a low tubular [K] so that K secretion remains robust. In this process, at least two forms of BK are involved – BK with the BK 1 (BK- / 1) and BK 4 (BK- / 4).

Localization of BK components

Several years ago, patch clamp analysis revealed the presence of BK in isolated, split-open, cortical collecting ducts of rabbits [18]. More recently, investigators revealed that iberiotoxin, a specific blocker of BK, inhibited flow-induced K secretion in either the micropunctured late distal tubule (connecting tubule; CNT) [34] or isolated perfused CCD [11]. Improved microscopy revealed that single BK currents were present in Na and K transporting principal cells (PC) but the majority of BK were in acid-base transporting intercalated cells (IC) [35]. Using immunohistochemical analysis, we subsequently showed that the BK 1 was expressed in the apical membrane of the mouse CNT and in the initial collecting ducts of the rabbit [9], whereas BK 4 was present with BK in IC [36]. As shown in figure 1, immunohistochemical analysis of a connecting tubule confirmed that BK is more densely expressed in IC, anti-AQP3 negative cells. BK- is less densely expressed in CNT cells, where BK 1 resides. Importantly, we determined that BK 4 was present in all IC, whether these were IC- , IC- , or non / -IC.

RT-PCR [37] and Western analysis [36] has identified BK 2 and BK 3 in the distal nephron, but their specific roles in K secretion have not been investigated. That BK KO, 1KO, and 4KO mice all have profound imbalances in electrolyte and volume management [7;33;38] is good reason to examine the K secretory roles of BK- / 1 and BK- / 4 in the CNT and IC.

BK- α / β 1, K secretion, and hypertension

Volume expanded mice with genetic deletion of only the BK 1 subunit (1KO) excrete substantially less K than wild type (WT) mice, indicating that BK- / 1 in CNT cells secretes K in response to flow [39]. These studies were performed when 1KO were anesthetized and the animals were perfused with physiological saline that included 5 mM K. However, the normal plasma [K] of mice on a normal diet is 4.1 mM [38]. An increase in plasma [K] from 4 to 5 mM can cause aldosterone-independent K secretion and a fairly large increase in aldosterone production [38;40;41], which can cause non-genomic increases in K secretion. A micropuncture study of ROMK knock-out mice confirmed that K secretion in the CNT occurs via an iberiotoxin-sensitive (BK) channel [34]. However, because flow and

plasma K were both increased in that study, the independent roles of aldosterone, high plasma K and flow, on the activation of BK- / 1 are still not understood.

We further investigated the role of BK- / 1 in electrolyte and volume balance utilizing 1KO on diets with varying quantities of K. When WT and 1KO were fed a high K diet (5% K, 0.3% Na) the urinary flows of both increased by 4.5-fold, consistent with its loop inhibiting effect; however, 1KO excreted 20% less K than WT.

A significant change in volume balance and blood pressure best illustrates the relevance of the 1KO defect in K secretion. Catheterization measurements determined that 1KO were hypertensive by 20 mmHg (mean arterial pressure: MAP) and the heart size was significantly increased, compared to WT, on a normal diet [42]. We repeated these studies measuring blood pressure with the tail cuff method and found that 1KO had a MAP of 21 mmHg above WT [38]. The hypertension of 1KO was exacerbated when mice were placed on a high K diet and mitigated when fed a low K diet (figure 2A). The failure of high K fed 1KO to secrete K at a substantial rate led to increased plasma [K], which stimulated aldosterone production with ensuing Na and fluid retention. Removing the fluid with eplerenone, an aldosterone receptor blocker, reduced the MAP toward values observed in mice on a low K diet. Therefore, the hypertension of 1KO was mostly the result of fluid retention.

As shown in figure 2B, the high K induced hypertension observed in 1KO was reflected by increased heart weight (HW) per pre-diet body weight (BW). When the two groups were compared, we found a significantly elevated HW/BW in 1KO, compared to WT, on a normal diet, as shown previously by Brenner et al [42]. When the multiple groups were compared, we found that the HW/BW of 1KO was further increased when mice consumed a high K diet and reduced to values not different from those of WT when treated with either a low K diet or adding eplerenone with the high K diet.

The eplerenone experiments showed that fluid retention has a major role in the elevated MAP of 1KO; however, sympathetic tone has a synergistic effect with fluid retention. In anesthetized mice, catheterization determined that MAP of 1KO was only 11 mmHg greater than WT. MAP values for 1KO were greater in awake, compared with anesthetized mice, indicating that sympathetic stimulation contributes to the hypertension. Nevertheless, in the absence of fluid retention, the hypertension of 1KO is very mild, with an MAP of only 7 mmHg above control, a small value compared with 33 mmHg above control in 1KO on a high K diet. This could explain why diuretic therapy is the most effective treatment for hypertension and why the only discovered monogenic forms of hypertension have been of the renal-adrenal axis [43].

To date, BK 1 polymorphisms have not been linked to hypertension; however several studies have revealed significant protection from hypertension in the gain-in-function BK 1 Glu65Lys mutant, which enhances the Ca sensitivity of BK when associating with the BK [44–46]. It will be interesting to determine whether an enhanced ability to excrete a K load and the prevention of Na and fluid retention are hallmarks of this resistance to hypertension.

It was also interesting that 1KO placed on a low Na diet were unable to retain Na and fluid as WT, leading to severe hyponatremia and hemoconcentration [47]. The mechanism involved was not determined; however, the appearance of the BK- / 1 in the basolateral membrane of WT on a Na deficient diet indicated that the BK- / 1 has a role to enhance Na reabsorption in the CCD when Na delivery is very low. Moreover, Na deficient 1KO were still slightly hypertensive, by approximately 7 mm Hg [21], compared to Na-deficient WT. It is possible that a pressure natriuresis results in the inordinate loss of Na in the Na-deficient 1KO.

Role of BK- $\alpha/\beta 4$ in IC in flow-induced K secretion

We were surprised at the predominant localization of BK- $\alpha/\beta 4$ in IC. IC are plastic cells with a variety of phenotypes - the acid-secreting IC- and base-secreting IC- are readily identifiable by immuno-identification of H-ATPase on the apical or basolateral membranes, respectively. However, IC-non- /non- , primarily in the CCD, have a more ambiguous phenotype with predominant cytoplasmic staining for H-ATPase. IC-non- /non- can transform to IC- or IC- depending on the acid/base status of the organism [48]. The IC- and IC- have different Cl concentrations of approximately 45 mM and 10 mM [49], and basolateral membrane potentials of -35 mV and -60 mV, respectively, [50]. Because IC- and IC- have such diverse properties, it would not be surprising if BK- $\alpha/\beta 4$ has different physiological roles in these cells.

Studies of isolated CCDs perfused with high flows demonstrate that the BK channels in IC must be playing a role in flow-mediated K secretion [11]. However, the IC contains a very low level of Na-K-ATPase compared with PC [33;51–53]. Unlike PC, the quantity of Na-K-ATPase in IC does not increase with a high K diet [33]. In the absence of a source of substantial K delivery, and because the BK channel is closed at resting potentials, it was originally considered a volume regulatory channel in renal cells [54]. This was difficult to assess directly without a cell culture model of IC that expressed BK that could be studied at the single channel level.

MDCK-C11 cells (C11) are specific IC clones with many IC properties [55;56]. Like all cultured cells, C11 do not replicate entirely the known properties of IC; however, BK- $\alpha/\beta 4$ are expressed in C11 apical membranes [57]. We determined that C11 exhibit BK- $\alpha/\beta 4$ dependent volume reduction in response to high shear stress [57]. This phenomenon was also investigated *in vivo*. Normally, IC are larger than PC and protrude into the lumens of CNTs and CCDs from WT mice on a control diet. However, when WT are fed a high K diet, the increased urinary flow is accompanied by a reduction in IC size. Flow in high K fed 4KO was reduced by 30% with little reduction in IC size. These results indicated that the reduction in IC size also reduces tubular resistance and enhances luminal flow. The enhanced flow was estimated to increase the chemical gradient for K secretion by 30%.

4KO also retain fluid [33] and are slightly hypertensive [21]. The fluid retention, but not the hypertension, is exacerbated by high dietary K. When fed a high K diet, 4KO also exhibit slight hyperkalemia and aldosteronism, but this may not explain their considerable Na and volume retention. A recent study suggested that an inability of IC from 4KO to secrete ATP may have a role in the Na retention [58]. Luminal ATP inhibits ENaC-mediated Na reabsorption in the CCD [59;60]. ATP is secreted from intercalated cells, as well as other cells [61–64], in response to high fluid flow. In MDCK-C11, secreted ATP serves as a counter-anion to the K secreted via apical BK- $\alpha/\beta 4$, as indicated by the reduced ATP secretion when applying BK- $\alpha/\beta 4$ siRNA. Moreover, high K fed 4KO exhibit a reduction in urinary ATP. As shown in figure 3, with high dietary K, the high flow is meant to stimulate the ratio of K secreted to Na reabsorbed. Reduced ATP secretion in response to flow can partially explain why 4KO exhibit enhanced Na reabsorption and fluid retention.

Future directions

The future of regulation of BK may relate to the WNK (With No Lysine) kinases, shown to distinguish between high aldosterone intended to enhance K secretion vs. high aldosterone intended to enhance Na reabsorption. WNKs, which phosphorylate SPAK, regulate NKCC, NCC, KCC, ENaC and ROMK [65–69]. However, more recent studies have implicated WNKs in the regulation of renal BK channels [70;71]. It will be interesting to determine the

role of WNKs in Na-independent K secretion, when Na reabsorption is very low and the demand for K secretion is very high.

Conclusions

BK channels are localized in the CNT as BK- / 1 in CNT cells and are localized in all IC cells of the CNT and CCD as BK- / 4. On a regular diet, 1KO are hypertensive by four different studies and the heart size is significantly increased compared with WT controls. When fed a high K diet for only ten days, flow is increased by over four-fold in mice in order to maintain low luminal [K] and maintain a concentration gradient for K secretion.

1KO accumulate fluid, are more hypertensive and heart size is greater when compared with WT. BK- / 4 in IC are activated by high flow-induced shear stress, with ensuing loss of intracellular K content and cell shrinkage, causing an increased luminal diameter and reduced resistance to flow. High flow induces negatively charged ATP secretion, coupled with K extrusion from IC. ATP extrusion in the distal tubule lumens enhances the ratio of K secretion to Na reabsorption by inhibiting ENaC-mediated Na reabsorption and activating BK- / 4-mediated K secretion.

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Key points

1. The physiological role of BK in the distal nephron is defined by its β -subunit.
2. The BK plays a pivotal role in renal K handling for maintaining volume balance and blood pressure.
3. Intercalated cells may have a larger role in Na/K balance than previous thought.

Figure 1.

Double immunohistochemical staining of renal section, highlighting a connecting tubule from a WT mouse on a normal diet, revealed predominant BK- (red) on intercalated cells (IC), marked by absence of anti-AQP3 (green), which highlights the basolateral membrane of CNT cells. Arrows indicate IC.

Figure 2.

Illustration of significance of findings with respect to hypertension. **A.** The hypertension of 1KO is exacerbated by a high K diet (HK) and alleviated with a low K diet (LK) or eplerenone (HK+E), demonstrating defective K handling and aldosteronism as the cause of hypertension [38]. **B.** Illustration of cardiac hypertrophy, measured by heart wt per pre-diet Kg body weight, in 1KO. Cardiac hypertrophy is exacerbated in 1KO on only ten days of HK diet and prevented by addition of eplerenone, which prevents fluid accumulation.

*P<0.05 compared with WT using the t-test for unpaired data. #P<0.02 compared with all groups using ANOVA plus Student-Newman-Keuls.

Figure 3.

Illustration of role of ATP in collecting ducts on Na and K transport. High flow induced by a high K diet initiates the release of ATP, a counter anion with the K loss in IC. ATP inhibits ENaC-mediated Na reabsorption and activates BK- / 4 causing an increase in the ratio of K excreted to Na reabsorbed.