



In Focus

The Colon as the Potassium Target: Entering the Colonic Age of Hyperkalemia Treatment?



Daniel Batlle*, Khaled Boobés, Kiran G. Manjee

Division of Nephrology & Hypertension, Northwestern University, Feinberg School of Medicine, Chicago, IL 60611, United States

Hyperkalemia is usually seen in patients with chronic kidney disease (CKD) when renal excretion of potassium (K^+) is reduced below the level of intake. Normal K^+ intake does not cause hyperkalemia despite a progressive fall in glomerular filtration rate (GFR) until a critically low level, usually less than 25 mL/min, is achieved (Batlle et al., 1981). This is due to adaptive mechanisms that permit the excretion of a normal daily K^+ load despite reduced GFR. Part of this adaptation involves the release of aldosterone from the adrenal glands. Aldosterone acts on the kidney promoting K^+ secretion. When the release of aldosterone is reduced — as in patients with idiopathic hypoaldosteronism or during the administration of renin angiotensin system (RAS) blockers or aldosterone antagonists — hyperkalemia often develops. In fact, the therapeutic use of these agents in patients with CKD, diabetic nephropathy or congestive heart failure is often limited by the development of hyperkalemia as a potentially dangerous side-effect. Since hyperkalemia usually develops as a result of reduced renal K^+ secretion, the question that arises is: can we rely on amplification of colonic K^+ excretion as a route of external disposal?

There are a number of similarities and differences between colonic and kidney K^+ secretion. Two types of apical membrane K^+ channels that permit K^+ secretion have been identified. The renal outer medullary K^+ channel (ROMK) is a low conductance K^+ channel which is present in the kidney (Wade et al., 2011; Frindt and Palmer, 2010). The large conductance K^+ channel (BK), is present in both principal and intercalated cells in the kidney (Najjar et al., 2005) and also in the colon (Sausbier et al., 2006). Aldosterone stimulates the Epithelial Sodium Channel (ENaC), causing a negative transepithelial potential and increasing the driving force for K^+ secretion via the ROMK channel. In the colon, the BK channel is the channel present in the apical site where it mediates K^+ secretion. There is also active transport of K^+ across basolateral membrane through Na-K-ATPase and Na-K-2Cl co-transport into cells. A negative potential difference across the colonic luminal membrane and the high intracellular K^+ also facilitate secretion of K^+ through the BK channel. K^+ absorption occurs in the distal colon as a result of active translocation of K^+ via a colonic H-K-ATPase.

The colon normally accounts for a small portion, about 5%, of total K^+ elimination, whereas the kidneys account for the remaining 95%. The colon, however, can become a significant site of K^+ excretion

when renal function decreases markedly. Similar to renal adaptive changes, colonic adaptive changes take place including: an increase in Na-K-ATPase activity, a rise in basal K^+ secretion and an increase in transmural potential difference. These changes are mediated by aldosterone-dependent and independent mechanisms. An increase in K^+ secretory capacity of rectal mucosa has been demonstrated in patients with advanced CKD (Sandle et al., 1986). While importantly, this natural adaptive increase in colonic K^+ secretion is not enough to prevent hyperkalemia. This K^+ secretory capacity, however, renders the colon a potential target for therapies aimed to treat and prevent hyperkalemia.

Two new colonic K^+ binders have shown efficacy in lowering plasma K^+ in recent clinical trials, thereby creating great expectations (Kosiborod et al., 2014; Packham et al., 2015; Bakris et al., 2015; Weir et al., 2015). How do these intestinal K^+ binders work? Under basal conditions, the K^+ absorptive process predominates in colon over the secretory process. Since in CKD the increased K^+ secretion in the colon is already an adaptive mechanism, limiting the amount of K^+ available for reabsorption in the distal colon is an effective way to eliminate this cation in the stool. K^+ binders make K^+ unavailable for absorption by trapping it within the binder molecule, which is then excreted with the feces. Carboxylic and sulfonic cation exchange resins have long been used to bind K^+ in the gastrointestinal (GI) tract. Kayexalate (sodium polystyrene sulphonate) is in wide use to manage hyperkalemia but usually is given acutely or short-term because of concerns with its side effects. To prevent constipation and increase Kayexalate's efficacy, sorbitol, an osmotic laxative, is often co-administered. The mixture with sorbitol at high concentrations, however, carries a risk of colonic necrosis and other serious GI adverse events.

Zirconium Silicate (ZS) and Patiromer are two new K^+ binders being introduced to manage hyperkalemia that do not require co-administration of sorbitol and promise to be more effective than Kayexalate. Due to its pore size and composition, ZS can mimic the high selectivity of physiological K^+ channels. This explains the >25-fold selectivity of ZS for K^+ over divalent cations such as Ca^{2+} or Mg^{2+} . ZS can effectively trap K^+ , starting slowly from very low gastric pH, while rapid and sustained K^+ uptake occurs as the pH increases in the colon where K^+ concentrations are higher. Patiromer has a novel chemical composition that promotes ionization of polymeric K^+ -binding moiety under pH conditions present along the GI tract using Ca^{2+} in cation exchange (Bakris et al., 2015; Weir et al., 2015).

* Corresponding author.

E-mail address: d-batlle@northwestern.edu (D. Batlle).

It exchanges monovalent (Na^+) and divalent cations (Ca^{2+} or Mg^{2+}) throughout the GI tract but preferentially binds K^+ in the colon with a net effect of facilitating its fecal excretion (Weir et al., 2015). While the rationale for these new binders is sound, additional information on mechanism of action and impact on colon K^+ transporters as well as evaluation of possible interactions with other drugs would be welcomed.

In short and long-term studies involving patients on concomitant RAS therapy, both ZS and Patiromer have been found effective in lowering plasma K^+ as compared to placebo. Neither compound, however, has been compared to Kayaxalate in terms of efficacy. By facilitating fecal K^+ excretion, these new binders are likely to open new venues for the treatment and prevention of hyperkalemia in high-risk patients, such as those in need of long term therapy with RAS-blockers and aldosterone antagonists for cardiovascular and kidney disease. With the new binders these therapies may be extended to patients, in whom concerns with hyperkalemia have precluded their use. We may be entering a new age: the colonic age of the treatment and prevention of hyperkalemia. This may bring clinical benefits for patients who otherwise could not tolerate RAS blockers and/or aldosterone antagonists and perhaps ease the strict K^+ dietary restrictions that patients with end stage renal disease need to endure.

Disclosures

The authors declare no conflict of interest.

Dr. Battle is a consultant or scientific advisory board member for Otsuka, Relypsa, ZS pharma and Keryx Biopharmaceuticals. His research is funded by NIDDK.

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