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Targeting colonic BK channels: A novel therapeutic strategy against hyperkalemia in chronic kidney disease

Canales BK colónicos: una nueva estrategia terapéutica contra la hiperpotasemia en la enfermedad renal crónica



Dear Editor,

Hyperkalemia is a common electrolyte disorder frequently observed in patients with chronic kidney disease (CKD).¹ Once potassium (K⁺) ions are absorbed from the daily food intake,

they are predominantly distributed in the intracellular space than in the extracellular space.¹ Under physiological conditions, approximately 90% of the dietary K⁺ ions are excreted into the urine, while the remaining 10% are excreted into the feces. The prompt management of hyperkalemia is to temporarily shift the extracellular K⁺ ions into the intracellular space by insulin.¹ However, to fundamentally treat hyper-

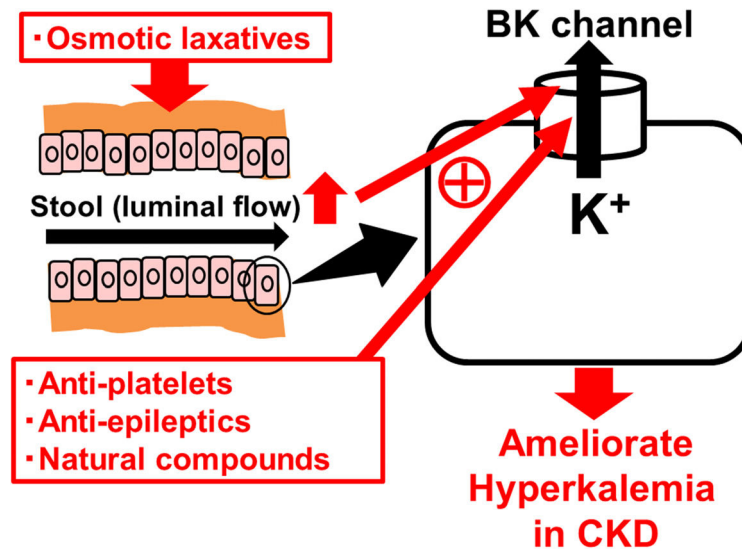


Fig. 1 – BK channels in colonic enterocytes as the therapeutic target for hyperkalemia in chronic kidney disease (CKD). BK channels are expressed in the apical membrane of colonic enterocytes and play a major role in excreting K^+ ions into the feces. Already marketed drugs, such as anti-platelets (cilostazol) and anti-epileptics (zonisamide), or natural compounds, such as estradiol, omega-3 docosahexaenoic acid (DHA) and resveratrol, increase the BK channel activity. Osmotic laxatives, which increase the intestinal luminal flow, also activate the BK channels and thus ameliorate hyperkalemia in CKD.

kalemia, the redundant K^+ ions have to be eliminated from the body, either by the use of diuretics to facilitate the renal K^+ excretion or by performing emergent hemodialysis.¹

In the kidneys, two populations of K^+ channels are expressed in the apical membrane of the collecting duct principal cells.² These channels, such as the renal outer medullary K^+ channels (ROMK or $Kir_{1.1}$) and large-conductance calcium-activated potassium channels (BK or $Kca_{1.1}$), play major roles in excreting K^+ ions into the urine. Both K^+ channels are directly stimulated by aldosterone and also by the decrease in the luminal K^+ concentration and the increase in the distal sodium (Na^+) delivery.² Of note, BK channels are additionally stimulated by the increased renal tubular flow,³ since this elevates the intracellular calcium (Ca^{2+}) concentration, which is the primary trigger of the channel activation. In patients with CKD, due to the renal tubular damage or dysfunction,¹ these K^+ channels are frequently disabled. Consequently, the impaired renal K^+ excretion leads to the much higher prevalence of hyperkalemia than in the general population.¹

Similar to the renal collecting ducts, BK channels are also expressed in the apical membrane of colonic enterocytes and play a major role in excreting K^+ ions into the feces⁴ (Fig. 1). In diseases that cause secretory diarrhea, such as ulcerative colitis, enteric infections, villous adenoma, BK channels are over-expressed or over-activated in the colonic epithelial cells,⁴ resulting in the increased fecal K^+ losses. In CKD, to compensate for the decreased renal K^+ excretion, its fecal excretion was alternatively increased.⁵ In clinical studies, since colonic BK channels were actually over-expressed in patients with advanced CKD or end-stage renal disease (ESRD),⁵ these channels were thought to be primarily responsible for the increased fecal K^+ excretion. Therefore, drugs that directly stimulate the colonic BK channels would be effective in the treatment of hyperkalemia in CKD.

So far, several BK channel openers, including NS1619, NS11021 and BMS204352, have newly been synthesized.⁶ Additionally, recent studies revealed that already marketed drugs, such as anti-platelets (cilostazol) and anti-epileptics (zonisamide)⁶ or natural compounds, such as estradiol, omega-3 docosahexaenoic acid (DHA) and resveratrol,^{6,7} also increase BK channel activity (Fig. 1). Besides the kidney and distal intestine, BK channels are also expressed in the cardiovascular system and central nervous system.⁶ Therefore, in using BK channel openers, the adverse effects on these organs need to be carefully monitored. However, compared to the highly selective, newly synthesized BK channel openers, the already marketed drugs or natural compounds could be used more harmlessly, because they have commonly been used in clinical practices or consumed in daily diets for longer periods of time. To increase the efficacy of these drugs or compounds after orally administered, they need to target the colonic BK channels as specifically as possible. In this regard, recently developed “drug delivery systems” that effectively reach the colon may be beneficial.⁸ They include pH sensitive system, microbially triggered system, prodrugs, polysaccharide-based system, timed-release system, osmotically controlled drug system and pressure-dependent release system.⁸

In CKD patients, chronic constipation is one of the risk factors for developing hyperkalemia,⁹ since it mechanically disturbs the fecal K^+ excretion. However, dissolving the constipation by probiotics alone did not ameliorate hyperkalemia in these patients. One of the commonly used laxatives, bisacodyl, is also a stimulator of BK channels,¹⁰ since it pharmacologically activates a cyclic adenosine monophosphate (cAMP). In CKD patients with hyperkalemia, the treatment with bisacodyl not only improved constipation, but also increased fecal K^+ excretion and actually ameliorated hyperkalemia.¹⁰ Among laxatives, osmotic laxatives, such as

magnesium hydroxide, polyethylene glycol, sorbitol and lactulose, exert their properties by drawing water into the colon and allowing easier and faster passage of the stool. In addition to the passive paracellular K⁺ excretion,¹⁰ such-induced increase in the intestinal luminal flow would activate the colonic BK channels (Fig. 1), similarly to the increased renal tubular flow that activates the renal BK channels.³ Given such pharmacological properties, the osmotic laxatives, which increase fecal K⁺ excretion through the activation of colonic BK channels, would also be beneficial in the treatment of hyperkalemia in CKD patients.

Conflict of interest

None declared.

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Comments: “Intervention study to verify the effect of live classic music during hemodialysis on the quality of life of patients with chronic kidney disease”

Comentario a «Estudio de intervención para comprobar el efecto de la música clásica en directo durante hemodiálisis sobre la calidad de vida de pacientes con enfermedad renal crónica»

Dear Editor,

We read with great interest the article by Serrano et al.¹ They show that listening to live music during hemodialysis treatment has a positive effect on the lives of patients with chronic kidney disease. The clinical trial focused on

evaluating descriptive variables, such as the etiology of kidney disease, hemodialysis treatment time, sex, age, vascular access by arteriovenous fistula or central venous catheter, mathematical expression Kt/V to measure the efficacy of hemodialysis treatment, consumption of psychotropic drugs and/or analgesic medication, serum hemoglobin (g/dl), serum albumin (g/dl), and mean arterial pressure (mmHg). A total of 90 patients participated in the clinical trial. They were orga-

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