Potassium intake to regulate sodium excretion? Don’t forget the anion.

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In the context of cardiovascular health, potassium has long been the forgotten cation, overshadowed by sodium occupying the “superior” position in the alkali metal series, Group 1 of the periodic table of elements. Epidemiological and interventional clinical trials are beginning to shift the dial, revealing health benefits of diets rich in potassium. The physiological mechanisms are not fully resolved. In this issue of *Acta Physiologica* a study by Vitzhum and colleagues shows that increasing dietary potassium intake in mice reduces the sensitivity of the distal nephron to the sodium-retaining hormone aldosterone. Intriguingly, the accompanying anion may be the critical factor(1).

The adverse health impact of high salt (NaCl) intake has long been recognised and dominates discourse related to modern dietary practice(2). Many countries have public health policies with aspirations to reduce salt intake. Dietary potassium does not garner the same attention, despite estimates that daily intake is habitually below the ~100mmoles/day threshold of adequacy(3). Indeed, when potassium is mentioned at all, it is common to caution against dietary overload and the risk of hyperkalaemia in people with kidney disease, or those taking mineralocorticoid receptor (MR) antagonists and renin-angiotensin system blockers(4).

The story is changing. Observational evidence associates higher potassium with reduced cardiovascular events, reduced mortality and lower albuminuria(5-7). Recent interventional studies show that substitution of regular table salt (100% NaCl) with “low-salt” (75% NaCl and 25% KCl) lowers blood pressure and reduces cardiovascular events; benefits that seem to reflect an increase in potassium intake rather than the reduction in salt intake(8, 9). Indeed, a metanalysis of randomised controlled trials finds that oral potassium supplements reduces systolic blood pressure by ~3mmHg, an effect size similar to that of monotherapy with front-line antihypertensive drugs(10).

The physiological mechanisms underpinning such benefit are not well understood. One possibility is that a potassium-rich diet facilitates sodium excretion by the kidney. Indeed, the diuretic properties of oral potassium salts have long been recognised and the effect of potassium intake on kidney sodium transporter function has been a subject of intense research in the last decade. For example, NCC is the sodium chloride cotransporter in the apical membrane of the distal convoluted tubule and the target of thiazide diuretics(11). It is now widely accepted that provision of oral potassium deactivates NCC(11), (12). The intracellular mechanism is delineated: elevated extracellular potassium increases intracellular chloride concentration, directly inhibiting the kinase WNK4 to dephosphorylate NCC and reduce expression in the apical membrane of the distal tubule cell(13).

Overall, this generates the concept that high potassium intake will drive extracellular potassium concentration to the top of its physiological range, exerting a thiazide-like effect on sodium excretion, thereby reducing extracellular fluid volume and blood pressure. However, the role of the aldosterone-sensitive distal nephron segments downstream of NCC remain unresolved. Sodium reabsorption in these segments increases with sodium delivery. Transport here is strongly stimulated by corticosteroid-induced activation of MR, which acts as a transcriptional regulator to the cell's sodium retaining machinery. When plasma potassium rises, after a K-rich meal for example, zona glomerulosa cells in the adrenal gland depolarise to promote aldosterone secretion. This should, at least in theory, promote sodium reabsorption through the epithelial sodium channel, ENaC. There lies the conundrum: high potassium intake clearly deactivates NCC but why is the sodium "lost" to the distal convoluted tubule not "found" again by downstream ENaC? This is not fully explained and here Vitzhum and colleagues tested the hypothesis that high potassium intake exerts a restraining

action on mineralocorticoid-induced stimulation of ENaC in the principal cell of the aldosterone-sensitive distal nephron(1). Using male C57BL mice, the authors confirmed the paradigmatical response of the ASDN to high salt intake with unchanged potassium intake: plasma aldosterone was supressed and in the principal cell, MR immunolocalization in the nucleus relative to the cytoplasm was reduced, indicative of diminished receptor activation/translocation. Functionally, the natriuretic response to amiloride, an ENaC-blocker, was abolished and at the protein level, there was coherent loss of apical membrane ENaC expression and reduced overall abundance in the principal cell.

Turning to their hypothesis, the authors challenged another group of mice with the same high salt intake but this time the diet was presented with a ~5-fold enrichment in potassium chloride content. Now the suppressive effect of high salt intake on aldosterone was completely lost and plasma levels were similar to those found in sodium-restricted mice. Despite this, the aldosterone-sensitive distal nephron did not activate its sodium-retaining machinery: MR did not translocate to the principal nucleus, ENaC abundance remained low and was not expressed in the apical membrane of the principal cell; functionally, there was no natriuretic response to amiloride. In a final series of experiments, Vitzhum *et al* examined the role of the accompanying anion, presenting mice with high salt diet supplemented with either potassium citrate or potassium chloride. Aldosterone was again stimulated in both groups despite the sodium-rich diet but in animals receiving K-citrate, principal cells of the ASDN showed full engagement of MR signalling and molecular activation of ENaC. Functionally, there was robust ENaC-mediated sodium reabsorption, despite the high salt intake. This inappropriate re-engagement of aldosterone action cannot be attributed to differences in plasma potassium. Nor is it likely that angiotensin II is

stimulated by hypovolemia in the K-citrate groups there being no rise in hematocrit. The main difference in measured variables was a significantly (~5mmol/l) lower plasma chloride in animals maintained on the high salt, potassium citrate diet.

To directly assess the role of chloride, the authors turned to a mCCDcl1 cells, an immortalised principal cell model. Cells were polarised as an epithelial monolayer and exposed to 30nmol/l aldosterone for 24h. In normal cell media (115mmol/l chloride), MR translocated to the nucleus. Cells grown in a higher chloride of 128mmol/l did not respond to aldosterone and there was no significant increase in MR translocation.

Epidemiological and clinical research demonstrates the cardiovascular health benefits of potassium-rich diets. Potassium supplementation, already used for the clinical management of hypokalemia, may help improve the cardiovascular risk profile in kidney disease and early reports suggest the approach is safe and well tolerated(14). Whether safety or efficacy is modified by the accompanying anion is largely unknown. Physiological studies in humans, old and new, show that the anion influences potassium's distribution between body compartments and the rate at which a potassium load can be excreted by the kidney(15). This fascinating study by Vitzhum and colleagues provides new knowledge, showing that the efficacy of high potassium intake to modify sodium transport in the kidney may be dependent on the anion(1). This physiological insight has important translational ramifications as "K-tablets" edge ever closer to clinical utility in long-term conditions such as chronic kidney disease.

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