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Loop diuretics are K⁺-sparing in the presence of a low-Na⁺, high-K⁺ diet

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Abstract

Under most conditions, loop diuretics are K⁺-wasting, requiring potassium supplementation. In this issue, Wang and colleagues demonstrate that in mice fed a low-Na⁺, high-K⁺ diet, loop diuretics, in contrast, are K⁺-sparing. This observation suggests that possible elevations in plasma K⁺ should be monitored when using a loop diuretic with a low-Na⁺, high-K⁺ diet, particularly when in combination with a potassium supplement.

The diets of early humans and ancestral hominids and primates were plentiful in plant matter rich in potassium (K) and poor in sodium (Na).^{1,2} As a result, humans, as did most mammals, evolved to be good at retaining sodium and excreting potassium.

Most people in developed countries now consume a diet far richer in sodium and poorer in potassium. This modern diet has been linked to increased incidences of hypertension.^{1,3,4} Current thinking is that a diet rich in sodium and poor in potassium contributes to elevated blood pressure because a kidney adapted to retaining sodium and excreting potassium is poorly prepared to excrete sodium when challenged with the high Na⁺ load of a modern diet.

Often in complement with dietary changes, such as a return to a low-Na⁺, high-K⁺ diet, diuretics are commonly used in the treatment of hypertension and other cardiovascular ailments including congestive heart failure because they disrupt the ability of the kidney to reabsorb Na⁺ and concentrate urine, resulting in an increase in urinary volume excretion and a dependent decrease in blood pressure. Some of the most powerful diuretics are loop diuretics, including furosemide, which target the luminal tri-transporter (NKCC2) in the thick ascending limb (TAL).

Typically, plasma K⁺ levels are fine-tuned by K⁺ secretion in the aldosterone-sensitive distal nephron.^{1,5} This is because with a modern diet, the bulk of the filtered load of K⁺ is reabsorbed by the proximal tubule and TAL.

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DISCLOSURE

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Potassium recycling across the luminal and serosal plasma membranes is critical for Na^+ reabsorption by the TAL. A lessening of Na^+ reabsorption by the TAL by any means, be it from a loop diuretic that inhibits NKCC2 or a genetic disease that impedes K^+ recycling, diminishes concentrating ability, causing an increase in urine volume excretion.⁶

Potassium recycles across the apical membrane of TAL epithelial cells via influx on NKCC2 and efflux via the renal outer medullary K^+ (ROMK) channel ($\text{K}_{\text{ir}}1.1$; KCNJ1). Potassium recycles across the serosal membrane via influx on the Na^+/K^+ -ATPase and efflux via $\text{K}_{\text{ir}}4.1/5.1$ channels (KCNJ10/16). Together these recycling pathways along with serosal ClC-K Cl^- channels (CLCNKA and KB) generate electrochemical gradients favorable to NaCl reabsorption at the TAL, allowing urinary concentration.^{1,5,6}

Because loop diuretics inhibit NKCC2, they abolish NaCl reabsorption at the TAL, destroying concentrating ability, and increase urinary flow and Na^+ delivery to the connecting tubule (CNT) and collecting duct (CD) system. Potassium secretion in these latter segments of the nephron is tied in a positive manner to urinary flow and Na^+ reabsorption.^{1,6} Consequently, loop diuretics commonly cause flow-induced K^+ secretion at the CNT and CD. This secondary effect of loop diuretics leads to their K^+ -wasting action. This is the reason why K^+ supplementation is often required when treating with loop diuretics. This mechanism also contributes to the K^+ -wasting common to many inheritable tubulopathies to include apparent mineralocorticoid excess, Bartter, EAST, Geller, and Liddle syndromes.⁶

In this issue Wang *et al.*⁷ (2017) report that in the presence of a diet more reminiscent of that consumed by earlier humans and their ancestors, rich in K^+ but poor in Na^+ , the TAL contributes significantly to K^+ secretion. This is in stark contrast to the K^+ reabsorption by the TAL present with a modern diet.^{1,7} Because the activities of NKCC2 and ROMK are elevated by a low- Na^+ , high- K^+ diet and this diet forms an electrochemical gradient that favors K^+ secretion at the TAL, loop diuretics become K^+ -sparing.¹ Again, this is in stark contrast to the more commonly observed K^+ -wasting action of loop diuretics. This switching from K^+ -wasting to K^+ -sparing also stands in contrast to the effect loop diuretics have in the presence of a high- K^+ -only diet.⁷⁻⁹

Previous studies have argued that a high- K^+ -only diet decreases rather than increases NKCC2 activity.⁸ Consequently, loop diuretics have little effect on K^+ excretion in the presence of a high- K^+ -only diet. In contrast, NKCC2 and ROMK activity are enhanced by a low- Na^+ , high- K^+ diet, and electrochemical gradients favor K^+ secretion with this latter diet resulting in loop diuretics being K^+ -sparing with this latter regimen.⁷

With a low- Na^+ , high- K^+ diet, loop diuretics still cause a profound diuresis because NKCC2 is actually more active with this diet.⁷ Similarly, the consequent increase in urinary flow and Na^+ delivery to the CNT and CD caused by loop diuretics in the presence of a low- Na^+ , high- K^+ diet results in flow-induced K^+ secretion at the CNT and CD. However, in the presence of a low- Na^+ , high- K^+ diet, the loss of K^+ secretion at the TAL in response to the actions of loop diuretics is quantitatively larger than the dependent increase in flow-induced K^+ secretion at downstream nephron segments, resulting in a net K^+ -sparing effect.

The exact cellular and molecular mechanisms that decrease and increase NKCC2 activity in response to a high-K⁺-only versus a low-Na⁺, high-K⁺ diet, respectively, are obscure at this time. Differences in angiotensin II signaling, though, may be involved. Angiotensin II regulates NKCC2 activity and increases in response to a decrease in blood volume resulting from low dietary Na⁺. Perhaps not coincidentally, angiotensin II levels are greatly increased in mice on a low-Na⁺, high-K⁺ diet but not on a high-K⁺-only diet.^{1,7}

That loop diuretics can be K⁺-sparing when provided in the presence of a low-Na⁺, high-K⁺ diet may remove the need for K⁺ supplementation. Moreover, monitoring for hyperkalemia is advised when treating with loop diuretics on a low-Na⁺, high-K⁺ diet, particularly in the presence of a K⁺ supplement.

REFERENCES

1. Cornelius RJ, Wang B, Wang-France J, Sansom SC. Maintaining K⁺ balance on the low-Na⁺, high-K⁺ diet. *Am J Physiol*. 2016;310:F581–F595.
2. Oliver WJ, Cohen EL, Neel JV. Blood pressure, sodium intake, and sodium related hormones in the Yanomamo Indians, a "no-salt" culture. *Circulation*. 1975;52:146–151. [PubMed: 1132118]
3. Appel LJ, Brands MW, Daniels SR, et al. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. *Hypertension*. 2006;47:296–308. [PubMed: 16434724]
4. Geleijnse JM, Kok FJ, Grobbee DE. Impact of dietary and lifestyle factors on the prevalence of hypertension in Western populations. *Eur J Public Health*. 2004;14:235–239. [PubMed: 15369026]
5. Welling PA. Roles and regulation of renal K channels. *Annu Rev Physiol*. 2016;78:415–435. [PubMed: 26654186]
6. Stockand JD. Renal ion channels, electrophysiology of transport, and channelopathies In: Alpern RJ, Caplan MJ, Moe OW, eds. *Seldin and Giebisch's The Kidney Physiology and Pathophysiology*. 5th ed. Amsterdam, Netherlands: Elsevier Inc.; 2013:217–262.
7. Wang B, Wen D, Li H, et al. Net K⁺ secretion in the thick ascending limb of mice on a low-Na, high-K diet. *Kidney Int*. 2017;92:864–875. [PubMed: 28688582]
8. Stokes JB. Consequences of potassium recycling in the renal medulla. *J Clin Invest*. 1982;70:219–229. [PubMed: 6284797]
9. Welling PA. Regulation of renal potassium secretion: molecular mechanisms. *Semin Nephrol*. 2013;33:215–228. [PubMed: 23953799]