Less Potassium Coming Out, Less Sodium Going In
Phenotyping ROMK Knockout Rats

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The Dahl salt-sensitive rat represents a widely studied model of salt-sensitive hypertension. In the current work, Zhou et al. phenotype a renal outer medullary potassium channel (ROMK) homozygous (−/−) and heterozygous (+/−) knockout rat on a Dahl salt-sensitive background. The authors performed a series of hemodynamic and metabolic studies to address the effects of genetically manipulating ROMK in the Dahl salt-sensitive rat. This model represents a major advance in tools available to study the role of ROMK in renal development, Na homeostasis, and blood pressure regulation. It is another of a growing number of −/− rats generated by zinc finger nucleases, which will eventually replace the need to study −/− mice. For this reason alone, the study should be considered a major accomplishment, as the literature on renal physiology and blood pressure regulation mostly comes from rats, and our ability to study rats is far more sophisticated than it is for mice.

ROMK is expressed in the thick ascending limb of the loop of Henle (TALH) and principal cells of the collecting duct. Both segments play a critical role in salt homeostasis and therefore blood pressure. In the TALH, both transcellular and paracellular pathways are involved in salt reabsorption. Transcellular absorption occurs when Na+, K+, and Cl− enter the cells via the apical Na/K/2Cl cotransporter (NKCC2) and exit via Na+/K+ ATPase. ROMK, located in the apical membrane of the TALH, recycles K+ back to the lumen. The lumen-positive voltage created when K+ is recycled drives Na+ independently.4 Although ROMK is expressed in both the TALH and principal cells, Zhuo et al.2 attribute essentially all of the phenotype of the ROMK homozygous knockout (−/−) and heterozygous knockout (+/−) rats to alterations in thick ascending limb function.

The importance of sodium transport in the TALH is best evidenced by the so-called loop diuretics and by loss-of-function mutations. The loop diuretic furosemide inhibits the activity of NKCC2 and has been largely used to treat hypertension and to manage clinical situations of volume overload. Loss-of-function mutations in NKCC2 and ROMK cause Bartter syndrome type I and type II, respectively.5,6 Among other metabolic features, these syndromes are characterized by polyuria, salt wasting, and hypotension. However, abnormally elevated reabsorption of salt by the TALH has been implicated with the development of salt-sensitive hypertension.6,9

On a normal-salt diet, ROMK −/− pups showed similar characteristics to ROMK −/− mice including severe volume depletion and high mortality rate after day 14.10 In contrast, ROMK +/+ and ROMK +/+ pups did not exhibit significant differences in body and organ weights and blood electrolytes compared with that of their ROMK +/+ littermates. Together these data demonstrate that ROMK plays an important role in salt excretion. Given the strong link between K recycling and salt absorption in the TALH, the authors imply that this is likely because of effects on this segment. Similarly, studies in humans showed that individuals with ROMK heterozygous mutations have reduced systolic and diastolic blood pressure and are less likely to develop hypertension.11 Thus the ROMK +/− rat seems to be a good model of human disease.

Although the development of the ROMK −/− rat is of considerable interest in terms of salt wasting and blood pressure regulation, its real value may be in the area of renal development where it may open up new paradigms. ROMK −/− rats have a defective renal structure, and only a small percentage of them reach adulthood. These data show that ROMK is not only important in NaCl absorption by the TALH, but it is required for proper development of the kidney. The influence of ROMK on development may be related to its role in NaCl absorption or K secretion, or it may be completely independent of its function as a transporter. This could be because of changes in either the TALH or collecting ducts, a possibility not raised by the
authors. Although the role of ROMK in renal development is novel, the fact that K transport can influence development has been shown in other tissues.12

In contrast to −/− rats, ROMK +/+ rats have normal kidneys. Such data indicate that a single copy of ROMK is adequate for normal renal development. These animals also develop smaller increases in blood pressure and less renal injury when fed high salt, indicating that ROMK heterozygous mutations in Dahl salt-sensitive rats exert a protective effect. The results concerning renal damage are interesting. Although it may be that ROMK +/+ kidneys were protected because of the reduction in blood pressure, a potentially more interesting interpretation exists. That is, that the role ROMK plays in development is also responsible for the renal protection. This latter hypothesis can only be tested in the −/− rats that reach adulthood, and +/− animals.

The fact that the heterozygous mutation does not seem to cause any disturbance in kidney development but antagonizes salt sensitivity may indicate that expression and activity of ROMK can change over time, be modified by different stimuli/environment, or that ROMK plays distinctly separate roles in renal development and NaCl absorption/K secretion. Collectively, these findings strongly suggest that ROMK expression and activity might not be only regulated by genetic mechanisms.

Previous investigations in mice and humans suggested the physiological importance of ROMK on salt reabsorption and blood pressure regulation.7,10,11 The current findings are of particular interest not only because they add to previous knowledge but also because they show for the first time that disruption of ROMK channels lead to attenuation of salt-sensitive hypertension in the Dahl salt-sensitive rat model. The study by Zhou et al10 will surely contribute to the development of new pharmacological strategies to manage hypertension and other diseases caused by electrolyte disturbances, and may open new areas of research in renal development.

Disclosures
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References

Figure. Schematic representation of a thick ascending limb of the loop of Henle cell and a collecting duct principal cell. EnaC indicates epithelial Na+ channel; NKCC2, Na/K/2Cl cotransporter; and ROMK, renal outer medullary potassium channel.
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