Thiazide-sensitive Na\(^+\)-Cl\(^-\) co-transport by the aldosterone-sensitive distal convoluted tubule (DCT) is responsible for re-absorption of approximately 10% of filtered Na\(^+\) and Cl\(^-\). The considerable clinical importance of Na\(^+\) and Cl\(^-\) re-absorption by the DCT is illustrated by the therapeutic efficacy of thiazide diuretics and the clinical phenotype of Gitelman syndrome, caused almost exclusively by loss-of-function mutations in the thiazide-sensitive Na\(^+\)-Cl\(^-\) co-transporter (NCC). A gain-in-function of NCC occurs in pseudohypoaldosteronism type II (PHA-II; also known as Gordon syndrome or hereditary hypertension with hyperkalemia); however, this disorder is caused by mutations not in NCC but in two of the four WNK (with no K/lysine) kinases, so-named for the absence of a conserved catalytic lysine.

Since the seminal genetic study implicating WNK1 and WNK4 in PHA-II, an increasingly populous signaling complex has been uncovered, encompassing WNK1, WNK3, WNK4 and the downstream STE20/SPS1-related proline/alanine-rich kinase (SPAK) and oxidative stress-responsive kinase 1 (OSR1). WNK1, WNK3, WNK4 and SPAK all are coexpressed with NCC in the DCT. Elements of this pathway also regulate the Cl\(^-\) and volume sensitivity of all functional members of the cation-chloride co-transporter gene family, including NCC, the two Na\(^+\)-K\(^+\)-2Cl\(^-\) co-transporters (NKCC1 and NKCC2), and the four K\(^+\)-Cl\(^-\) co-transporters (KCC1 through 4). More recently, there are outlines of the interactions of this pathway with aldosterone and angiotensin-dependent regulation of NCC. Variation in the human
STK39 gene encoding SPAK is also associated with differences in BP. 7

Much of the work on WNK pathways exploits the coexpression of kinases with NCC in nonmammalian cells, specifically Xenopus laevis oocytes. Notably, however, key observations in this system predict the cellular and physiologic phenotype of WNK4 transgenic mice with overexpression of wild-type WNK4 and a disease-associated WNK4 mutation, 10 such that insights obtained are physiologically relevant.

There still are a number of controversies and discrepancies in the reported data 3,4,11; however, a consensus of results indicates that WNK4 coexpression inhibits NCC, with abrogation of this effect by PHA-II–associated mutations. WNK1 in turn has no effect on NCC but abolishes the inhibitory effect of WNK4. WNK3 coexpression activates NCC 3,4,11; a recent chimeric study localized the differential effect of WNK3 and WNK4 to the N-terminal 300 to 400 or so amino acids of the two kinases. 11 WNK-dependent activation of SPAK or OSR1 leads to phosphorylation of a cluster of N-terminal threonines in NCC, NKCC1, and NKCC2, resulting in the activation of Na+–(K+–Cl)− co-transport. 3,4

In this issue of JASN, Glover et al. 12 report an interesting twist in this intriguing story with their finding of dramatic differences in the effect of renal (R–WNK3) and brain (B–WNK3) alternatively spliced isoforms, again using coexpression with NCC in Xenopus oocytes. The two isoforms of this kinase differ in inclusion of two alternative versions of exon 18 and in the presence or absence of the 11-codon cassette from exon 22 (see Figure 1 of Glover et al. 12); this C-terminal variation thus affects only a tiny fraction of the approximately 1800 residues in the kinase.

Despite this modest difference in primary structure, R–WNK3 strongly activates the transporter and B–WNK3 strongly inhibits. Both kinases affect expression of the transporter at the membrane; however, whereas the effect of B–WNK3 seems to be dependent on SPAK, that of R–WNK3 is not. The effect of WNK3 and WNK4 on trafficking of the transporter does not require N-terminal phosphorylation of NCC, suggesting that SPAK-dependent phosphorylation increases intrinsic activity at the membrane.

Despite its many advantages, the use of Xenopus oocytes for these studies has acknowledged limitations. 4 In particular, overexpressed kinases may exert effects by sequestering, binding, or otherwise interfering with the endogenous signaling pathways of the oocyte, in this case the Xenopus laevis SPAK and WNK. Ideally, studies of this pathway should use a combination of heterologous expression and cellular models of the DCT. 9 Another concern is the failure to detect co-association of SPAK with WNK3 and NCC 12; all of the WNK kinases contain a specific interaction motif for binding to SPAK, as does NCC. 4

Why, then, is this new study 12 of interest, particularly if the brain WNK3 isoform is not expressed in kidney and thus not involved in the regulation of NCC? First, as noted by Glover et al., 12 their study emphasizes the need to consider not just tissue-specific expression but also tissue-specific alternative splicing when studying physiologic phenomena in a heterologous expression system. Second, this report is perhaps the first clean separation of SPAK-dependent and SPAK-independent effects of a WNK kinase on NCC. Undoubtedly, further complexity will follow, particularly when one considers the redundant, overlapping regulation of the epithelial sodium channel as a model for the regulation of distal salt transport. 1

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DISCLOSURES

None.

REFERENCES

10. Lalioti MD, Zhang J, Volkman HM, Kahle KT, Hoffmann KE, Toka HR,
How Long Can We Afford to Wait for Equity in the Renal Transplant Waiting List?

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“I used to think I was poor. Then they told me I wasn’t poor. I was needy. Then they told me it was self-defeating to think of myself as needy. I was deprived. Then they told me underprivileged was overserved. I was disadvantaged. I still don’t have a dime. But I have a great vocabulary.”


Although “a rose by any other name would smell as sweet,” poverty and its magnified impact on health outcomes in the absence of universal health care, by any other name, remains a souring indictment of the moral compass of the wealthiest nation on earth. Nephrology is one of the first subspecialties to recognize disparities in the prevalence of one of its key areas of care, ESRD.1 More recently, nephrology has witnessed an awakening to understanding many of the underlying factors that contribute to ESRD,2–5 as well as addressing the quality of care for patients afflicted with chronic kidney disease (CKD) or ESRD, especially across racial and ethnic, gender, and income demographics.6,7 As Powe2 notes in his urge for us to take disparities seriously, when it comes to kidney transplants, white patients in 2004 were 30% more likely to receive a transplant within 2 yr than black patients and 20% more likely than Hispanic patients.

So then, why is it that more than 35 yr after Congress resolved the issue of reimbursement for dialysis and kidney transplantation by enacting the Social Security Amendments of 1972, black patients with ESRD remain less likely to be placed on waiting lists for kidney transplantation? In 2000, Furth et al.8 reported racial differences in access to the kidney transplant waiting lists for children and adolescents, and Wolfe et al.9 reported similar findings among adults. Keith et al.10 observed between January 2001 and December 2004 access to waiting lists for patients who had CKD and wanting cadaveric donor renal transplantation was markedly worse for patients with Medicare, racial and ethnic minorities, and those with low levels of educational attainment. In adjusted subgroup analyses for patients who are older than 64 yr, Medicare is no longer a risk for low access to waiting lists, likely because this is the cutoff point when Medicare eligibility restrictions are lifted; however, the large disparity in access to waiting lists for racial and ethnic minorities and those with low levels of educational attainment persists, suggesting that even for dialysis patients who benefit from a form of universal coverage, equity exists for many but not all services or conditions. Geographic variations in placement on waiting lists and kidney transplantation rates among patients with ESRD contribute to these racial disparities, with rural black individuals being less likely to be placed on the waiting list and undergoing transplantation than those who reside in urban areas in some studies11 but not all.12 Additional barriers to transplantation include but are not limited to distance from residence to a transplant center, religious beliefs, lower quality matches as a result of the limited availability of organs for transplantation, less access to care, increased number and/or severity of comorbid conditions, lack of family or social support, fear of specialized procedures at complex medical centers, lower likelihood to be rated as appropriate candidates for transplantation, lower chances of referral for evaluation, greater likelihood of incomplete evaluations, and facility-level effects.5,13,14

In this issue of JASN, Patzer et al.15 look beyond the traditional boundaries of clinical and social determinants of health that compose most traditional medical analyses to explore the role of neighborhood socioeconomic factors on health, specifically the likelihood of being placed on the waiting list for a kidney transplant. Using data for a cohort of 35,000 incident, adult patients with ESRD in ESRD Network 6 (Georgia, North Carolina, and South Carolina) and linking it to data from the United Network for Organ Sharing transplant registry through 2005 they find, in contrast to others, that the distance from patient residence to the nearest transplant center does not predict placement on the transplant waiting list. In fact, they found race, neighborhood poverty, gender, age, diabetes, hypertension, body mass index, albumin, and the use of erythropoietin on initiation of dialysis are more associated with placement on the waiting list. As neighborhood poverty increases,