The renal WNK kinase pathway: a new link to hypertension

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The discovery of the renal WNK kinase pathway is offering new insights into sodium, potassium and blood pressure regulation in the distal nephron. It has also largely explained the pathogenesis of a genetic form of hypertension called familial hyperkalaemic hypertension (FHHt, also known as pseudohypoaldosteronism type II or Gordon’s syndrome), because it is caused by mutations in WNK kinases. However, the question is: do the renal WNK kinases have clinical significance beyond this rare syndrome? Here, we review the most recent data on renal WNK kinase physiology and discuss their potentially broader roles in electrolyte transport and hypertension.

The renal WNK kinase pathway: current status

As so often in science, the identification of the WNK kinases was a serendipitous finding. In 2000, Xu et al. pursued a nested polymerase chain reaction cloning strategy to identify novel members of the mitogen-activated protein/extracellular signal-regulated protein kinase family [1]. Instead, they found a new member of the serine/threonine kinase family. They named the new kinase WNK, which stands for With No K, with ‘K’ referring to the amino acid lysine. The name highlights their unique characteristic: the location of the catalytic lysine crucial for binding to ATP in subdomain I instead of II, as is the case in all other protein kinases. To date, five WNK kinases have been identified, namely WNK1 through WNK4 and kidney-specific WNK1 (KS-WNK1, a second transcript from the WNK1 gene). The physiological functions of the WNK kinases are diverse and include cell volume regulation, neurotransmission, cell proliferation, embryonic development, paracellul-
electrogenic sodium reabsorption by ENaC, thereby increasing the transepithelial voltage and stimulating potassium secretion. The opposite occurs when a low sodium diet (hypovolaemia) does not affect or even decreases KS-WNK1 and WNK4, because this will activate the Na-Cl-cotransporter and favour electroneutral sodium reabsorption with a relative conservation of potassium.

**WNK kinases and hypertension**

The WNK kinases have attracted most attention as the cause of FHHt. Positional cloning studies of patients with FHHt revealed two causes [11]: intronic deletions causing the overexpression of wild-type WNK1 (which inhibits WNK4) and missense mutations causing mutant WNK4 (which inhibits wild-type WNK4 and fails to inhibit WNK3). Mice transgenic for mutant WNK4 [12] and knock-in mice with one mutant and one wild-type WNK4 allele [13] recapitulate the phenotype of FHHt. The rarity of FHHt raises the question if the WNK kinases have clinical relevance beyond this syndrome. To answer this question, we first address two other questions: is the current management of hypertension suboptimal and, if so, what is needed to improve it? In our opinion, the answer to the first question is clearly ‘yes’, because ~90% of the cases of hypertension are still considered to be ‘essential’ and treatment is largely trial-and-error. The answer to the second question logically follows from the first: better management of hypertension requires a better understanding of its pathogenesis and markers to determine the patient’s individual sensitivity to antihypertensive drugs. Can the renal WNK kinases contribute to this mission? We believe so and provide three examples. First, the renal WNK kinase pathway offers a potential mechanistic explanation for the association between potassium depletion and salt-sensitive hypertension [14]. Our diet has gradually changed from potassium-rich and sodium-poor in Paleolithic times to the opposite in modern times [15]. As noted, potassium restriction increases WNK1 and decreases KS-WNK1 in animals [7–9]. A decrease in KS-WNK1 will relieve its inhibition of WNK1, allowing it to either inhibit WNK4 and activate the Na-Cl-cotransporter (DCT) or to activate SGK1 and ENaC (CCT and CD, Figure 1). The result is increased sodium reabsorption at two nephron sites that will increase blood pressure. The second example is the association between hypertension and hyperinsulinaemia, a prominent feature of diseases such as diabetes mellitus and obesity. Song et al. showed that the rise in blood pressure in rats on chronic insulin treatment was likely due to enhanced sodium reabsorption by the Na-Cl-cotransporter and ENaC, because apical localization of ENaC subunits was increased and treatment with hydrochlorothiazide and amiloride resulted in increased natriuresis [16]. Interestingly, insulin reduced cortical WNK4 expression [16], which would indeed be expected to activate the Na-Cl-cotransporter and ENaC (Figure 1). The third example is that single nucleotide polymorphisms and haplotypes in WNK1 contribute to blood pressure variation in the general population [17], possibly mediated via effects on the gradient of blood pressure change with age [18]. Interestingly, the gene encoding for SPAK (STK39), which interacts with the WNK kinases (Figure 1), was also recently identified as a hypertension susceptibility gene in an Amish population [19]. The ability to predict individual predispositions to hypertension logically leads to the last unanswered question: are there biomarkers for hypertension? Screening for polymorphisms and haplotypes could be a useful clinical tool in the foreseeable future although the available tests have not found widespread use in clinical practice [20]. It has proven difficult to establish clear-cut associations between blood pressure polymorphisms (e.g. α-adducin, angiotensinogen, angiotensin-converting enzyme) and the risk of hypertension, cardiovascular events or responsiveness to therapy [21,22]. However, the modest effect of variants in a single gene may be explained by their interactions with related genes. Indeed, when variants in the genes for WNK1, α-adducin (influences activity Na-K-ATPase) and Nedd4-2 (ubiquinates ENaC) were combined, a significant effect was found on renal salt handling, the blood pressure response to saline and thiazides and nocturnal systolic blood pressure [23]. This being said, genes are still far off from the actual biological work force, namely proteins. Therefore, one would wish for a measure of Na-Cl-cotransporter, ENaC or WNK activity in the distal nephron. Because renal biopsies are not regularly performed in hypertensive patients, a logical alternative would be urine, because it contains many disease-associated proteins. Studies that proved this principle have demonstrated increased urinary excretion of
the Na-Cl-cotransporter in patients with FHHt [24] and a specific urinary pattern of the ENaC-activator prostanin in patients with primary aldosteronism [25]. These studies used whole urine, but a more targeted approach could be to use so-called urinary exosomes. Urinary exosomes are the internal vesicles of multivesicular bodies secreted by renal epithelial cells and contain the Na-Cl-cotransporter and ENaC (it is not known if WNK kinases are present in exosomes) [26]. Urinary exosomes have not been analysed in hypertensive disorders, but their utility is illustrated by the identification of exosomal biomarkers that are capable of predicting acute renal failure prior to a rise in serum creatinine [27,28].

**Perspectives**

The role of the renal WNK kinases and their interactions with sodium and potassium transporters in the rapidly evolving cell models of the DCT, CNT and CD is becoming increasingly clear. Nevertheless, the roles of WNK3 and especially WNK2 in the distal nephron are relatively unknown. In addition, biology is never as simple as a single protein family, and at least three kinase systems appear to coordinate signal transduction from receptor to transporter, including the WNK kinases, SGK1 and SPAK/OSR1 (Figure 1). Although aldosterone is an indisputable activator of WNK kinases, it is unknown if other hormones acting on the distal nephron such as vasopressin, angiotensin II and atrial natriuretic peptide are also capable of regulating the WNK kinases. The first animal studies have focused on aldosterone and WNK kinases, but a complete picture likely also requires the analysis of other circulating hormones, the related receptors and transporters and, of course, blood pressure. Apart from physiological insights, it seems logical to pursue the quest of finding urinary biomarkers for hypertension [29]. As of yet, the renal WNK kinases as drug targets is science fiction, but the example of the tyrosine kinase inhibitor imatinib for chronic myeloid leukaemia illustrates that it is not a priori impossible to selectively inhibit kinase systems [30,31]. The feasibility to inhibit WNK1 was also illustrated in mice heterozygous for the WNK1 mutation, which showed a marked reduction in blood pressure without apparent side effects [32]. Hypertension is obviously a multifactorial and complex disease, but the WNK kinase pathway is opening an attractive avenue to better understand and potentially diagnose and treat hypertension.

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Intensifying dialysis: how far should we go and at what cost?

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In a recent issue of JASN, Lee and colleagues [1] presented the results of a simulation model estimating the cost-effectiveness of different modalities of centre-based dialysis, increasing frequency and/or duration. Their simulation shows that this intensified approach, even with—according to the authors—rather conservative assumptions about its benefit is associated with poor cost-effectiveness. None of the simulations resulted in a cost per quality adjusted life year (QALY) below $75 000. Generally, the societal threshold for the willingness to pay for gaining 1 QALY is around $50 000 as the authors confirm.

In other words, the extra money spent on the increased frequency and/or increased duration does not result in a proportionally acceptable health benefit. Spending this money elsewhere (for instance on better prevention of nephropathy, or on alternative non-centre-based types of dialysis) would bring much more benefit to society.

One could moreover argue that the assumptions are not that conservative at all: the rare evidence existing about this intensified care? Is it value for money? After all, its management [2].

In other words: ‘are we going to deny better care to these people for the reason of cost?’ I would rather talk about value than about cost. The real question is what is the value of this intensified care? Is it value for money? After all, the goal of health care is to produce health [3], and in any production process, one needs to aim for being productive, i.e. to produce the most possible output (here health) with the invested money. When a given production process is not productive, then we must not undertake it, because we

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