TRPV4: a new target for the hypertension-related kinases WNK1 and WNK4

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The “TRANSIENT RECEPTOR POTENTIAL” (TRP) super family of ion channel encompasses more than 50 cation-permeable channels that are expressed in many cells and tissues, from yeast to human. Most of the TRP channels are permeable to Ca\(^{2+}\), providing Ca\(^{2+}\) influx mechanisms. Based on structure and homology, the TRP superfamily can be subdivided into seven subfamilies (12), from which the TRPV (vanilloid) subfamily contains at least two members that turned out to be, or are emerging as, very important in renal physiology. TRPV5 is known to play a key role in renal transepithelial Ca\(^{2+}\) transport (11). TRPV4 was identified as the mammalian homolog of OSM-9, the key osmosensory channel in Caenorhabditis elegans. TRPV4 is activated by several stimuli, including thermal stress, the non-PKC-activating PMA analog 4\(-\)phorbol 12,13-didecanoate (4\(-\)PDD), and, most importantly, by hypotonicity (for a review, see Refs. 1 and 13). Because hypotonic stress is accompanied by Ca\(^{2+}\) entry that is required for upregulation of K\(^{+}\) and Cl\(^{-}\) efflux, it has been proposed that TRPV4 provides a signaling afferent pathway for cell volume regulation. In the kidney, TRPV4 is absent in the proximal tubule and descending limb, nephron segments with high water permeability, whereas its expression begins in the ascending thin limb and is continuous through the thick ascending limb, distal convoluted tubule, and collecting duct, which are nephron segments exhibiting absolute or conditional water impermeability (15). Interestingly, TRPV4 is absent in the macula densa, the only region of the thick ascending limb that is permeable to water. This nephron distribution, together with recent observations that TRPV4 null mice developed an impairment in osmotic sensing in the central nervous system (7, 9), strongly suggests that TRPV4 plays a central role in systemic osmoregulation. Because TRPV4 along the nephron is polarized to the basolateral membrane, it has been recently proposed that its major role could be to sense the changes in interstitial osmolality, as it is expected to occur with changes in urine flow rate (1).

In this issue of the American Journal of Physiology-Renal Physiology, the study by Fu et al. (3) describes the effect of the serine/threonine kinases “With No Lysine (K) Kinases” (WNK)1 and WNK4 on the activity and surface expression of TRPV4. These kinases are implicated in the pathogenesis of a salt-dependent form of human hypertension known as pseudohypoaldosteronism type II (PHAIIs) (17). The gene family is known as “With No Lysine (K) Kinases (WNKs)” because of the lack of the invariant catalytic lysine in subdomain II of protein kinases. Mutations in WNK1 resulting in PHAIIs are due to intrinsic deletions, producing overexpression of the kinase, whereas PHAIIs-causing mutations in WNK4 are missense mutations in an acidic domain of 10 residues, highly conserved in the 4 WNKs. The mechanism for the development of both hypertension and hyperkalemia in PHAIIs patients is beginning to be revealed by the findings that WNK4 regulates the activity of several plasma membrane transport proteins in the kidney, including the thiazide-sensitive Na\(^{+}\)-Cl\(^{-}\) cotransporter (NCC), the basolateral isoform of the bumetanide-sensitive Na\(^{+}\)-K\(^{+}\)-2Cl\(^{-}\) cotransporter (NKCC1), the Cl\(^{-}\)/HCO\(_3\)^{-} exchanger (CFEX), the inwardly rectifying K\(^{+}\) channel (ROMK), and claudins, tight junction proteins (for a review, see Ref. 4). Moreover, PHAIIs-like mutations in WNK4 alter the regulation of these transport pathways by WNK4. Other features of the disease, however, remain to be explained. This is the case, for example, of metabolic acidosis and hypercalciuria (8).

Fu et al. (3) used a transient expression of the TRPV4 channel in HEK293 cells to study the effect of WNK1 and WNK4 on TRPV4. They first observed that hypotonicity or 4\(-\)PDD resulted in a significant increase in TRPV4 activity, which was remarkably prevented by cotransfection of TRPV4 with WNK4. WNK1 had a similar effect, and WNK1 plus WNK4 did not exhibit synergistic effect. Previous studies have shown that WNK1 is able to regulate the activity of transport systems, such as NCC, NKCC1, or the epithelial sodium channel ENaC, but only through its interactions with other kinases like WNK4 (20), the STE-20-related kinase SPAK (10, 16), or the serum-glucocorticoid kinase SGK1 (19), respectively. Thus the fact that WNK1 by itself is able to downregulate the activity of TRPV4 is interesting. Together with a recent report on WNK1 effects on ROMK (6), these are the first direct evidences of the effects of WNK1 on transport systems. By using biotinylation experiments to assess cell surface expression of the channel, Fu et al. (3) demonstrated that reduction of TRPV4 activity in the presence of WNK1 or WNK4 correlated with a significant decrease in TRPV4 present in the plasma membrane. Puzzling results regarding the requirement of kinase activity in WNK4 and WNK1 were observed. The catalytically inactive WNK4 harboring the mutation D318A loses the inhibitory effect on TRPV4, whereas the catalytically inactive WNK1 mutants K233M or S378A still exhibited the inhibitory effect, suggesting that WNK4, but not WNK1 catalytic activity, is required for TRPV4 inhibition. In contrast, using WNK4 deletion mutants, the authors observed that in the absence of the kinase domain, the rest of WNK4 still inhibited TRPV4, whereas in the absence of the regulatory domain, WNK4 loses the inhibitory effect on TRPV4. Thus, although a point mutation that renders WNK4 catalytically inactive abrogated the negative effect of WNK4 on TRPV4, the deletion of the entire kinase domain did not, suggesting the intriguing possibility that the full-length, catalytically inactive WNK4 may be endowed with particular properties. Such a situation has been demonstrated to occur with the catalytically inactive form of WNK3 with reference to the regulation of the cation-coupled Cl\(^{-}\) cotransporters (2, 5, 14). Finally, although WNK4
harboring the PHAII missense mutations E599K or Q562E was still able to inhibit TRPV4 activity, the level of inhibition was significantly lower than for wild-type WNK4, suggesting that for TRPV4 inhibition, PHAII mutations behave as a “loss-of-function” type, similar to what occurs with NCC (18). The work of Fu et al. (3) adds a new transport system to the growing list of membrane transporters and channels that are regulated by WNKs and opens a possible pathway to begin understanding the origin of hypercalciuria in PHAII patients.

REFERENCES