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Sticky business: cytoskeleton and Na+ transport.

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Editorial

Great strides have recently been made in our understanding of human hypertension at the level of discrete genetic mutations. We now understand the pathophysiology of glucocorticoid-remediable aldosteronism (1), Liddle's syndrome (2), and the apparent mineralocorticoid excess syndrome (3). In each of these syndromes, inappropriate renal Na^+ retention with subsequent hypertension occurs through the agency of unusual mineralocorticoids, or in the case of Liddle's syndrome ("pseudoaldosteronism"), an apparent mineralocorticoid effect due to mutations which constitutively activate the amiloride-sensitive epithelial Na^+ channel. In each of these examples (1–3), the functional effects of these mutations have been confirmed in various expression systems.

These successes have relied on the candidate gene approach and clinical insights into the underlying pathophysiology. These successes are notable, but failures of the candidate gene approach go unheralded. At the same time, positional cloning efforts have been quite fruitful in identifying numerous loci of interest in hypertensive inbred rat strains. As a rule, these efforts have identified promising chromosomal intervals which contain genes of specific interest (e.g., inducible nitric oxide synthase), but precise mutational derangements have not yet been described. While these efforts hold great promise for identifying new candidate genes for human hypertension, considerable effort will be required to extend these findings to precise pathophysiologic understanding of human disease.

The report herein of Tripodi et al. (4) provides an important demonstration of the functional effects of mutations in accessory proteins which appear to regulate transepithelial Na^+ transport. Previous work from this group demonstrated that missense mutations in the α and β adducin subunits accounted for some of the blood pressure difference between the Milan hypertensive and normotensive strains of inbred rats (5). Their current findings demonstrate in vitro effects of these mutations on actin assembly and on Na^+ pump activity (measured as ouabain-sensitive $^{86}Rb^+$ uptake) in epithelial-like cells transfected with the relevant constructs, and grown on filter supports. Of note, there was no change in cell volume, so that increased Na^+ pump activity must have been associated with a corresponding increase of Na^+ entry into these cells. In fact, a primary effect on Na^+ entry pathways could well explain these findings since it well recognized that the rate of apical membrane Na^+ entry regulates the rate of transepithelial transport, and that enhanced Na^+ entry can chronically increase Na^+ pump activity (6).

While cytoskeletal elements do interact with Na^+-K^+-ATPase (7), of even greater interest is the interactions of actin filaments with the amiloride-sensitive epithelial Na^+ channel (8). These interactions may involve specific proline-rich domains of the cytoplasmic tails of the channel subunits (9) and involve various aspects of channel regulation, even including potential mechano-sensitivity (10). The latter finding re-affirms the suggested evolutionary relationship between the epithelial sodium channel subunits and the family of degenerins described as playing a role in mechanosenory transduction in *C. elegans* (11, 12). An important inference from the present studies is that members of the adducin family are involved in regulation of transepithelial Na^+ transport, and that missense mutations of various adducin subunits could account for inappropriate activation of apical membrane Na^+ entry, and thus enhance Na^+-K^+-ATPase activity and transepithelial Na^+ reabsorption. If such "constitutive activation" of apical Na^+ entry occurred in the face of dietary salt excess, then Na^+ reabsorption would be excessive. Such dysregulation of transepithelial Na^+ transport could be an important cause of volume expanded ("low-renin") hypertension. While it appears that mutations of the currently described subunits of the amiloride-sensitive Na^+ channel account for a very small proportion of human hypertension (13), the cytoskeletal arrays, including actin (7, 8), adducins (4), and other elements such as the profilins (14) provide a variety of candidate genes to be considered in relation to dysregulation of renal Na^+ reabsorption and the pathogenesis of low-renin or "salt-sensitive" hypertension.

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