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Perspectives

PERSPECTIVES

Uncovering the Complexities of Salt Sensitivity

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A Perspective on 'Endothelial Cullin3 Mutation Impairs Nitric Oxide-Mediated Vasodilation and Causes Salt-Induced Hypertension'

Historically speaking, the dangers of chronic high salt diets in Western culture is a relatively modern phenomenon. Throughout human history, empires were built and wars fought over access to large supplies of NaCl.[1] However, as we now know, too many people on our planet suffer a wide range of health problems that are exacerbated, if not caused by, high salt diets. The basic physiology of sodium homeostasis has some well-established mechanisms, but we continue to learn about the many complex and redundant systems that regulate this critically important cation that go beyond the basic renin-angiotensin-aldosterone system.

Control of sodium homeostasis and its contribution to disease has been an area of active research for over 50 years, primarily in the hypertension field and remains a critically important area of research. Furthermore, it is now clear that complications with many other organ systems can be attributed to high salt content in our diets.[2–4] In addition to salt-sensitive hypertension, this includes a diverse range of problems such as Alzheimer's disease and non-alcoholic fatty liver disease, or NAFLD. In all of these situations, the physiological mechanisms contributing to disease are multi-faceted and have not been resolved, especially since these complications are sometimes clear on a population level, but less clear on an individual basis. This degree of heterogeneity reflects a wide range of possible environmental, behavioral, or genetic causes. One common thread may be vascular or hemodynamic factors. Over the past 40 years, we now recognize the vascular endothelium as one of the most critical regulators that all organ systems depend on to maintain normal function.

One of the most important endothelial cell regulators of vascular tone is nitric oxide produced by the conversion of L-arginine to L-citrulline and NO via the NO synthase isoform, NOS3. Appropriate vasodilation and natriuresis are essential steps in preventing hypertension produced by high salt intake and that this system is less effective in some individuals who display salt-induced hypertension. The recent study of Wu and colleagues provides valuable new insights into how the endothelial cell, and specifically NOS3, is likely an explanation for at least some forms of salt-sensitive hypertension.[5] Prior studies have demonstrated that mutations in the gene encoding Cullin3 (CUL3) cause familial hyperkalemic hypertension. CUL3 provides the structural backbone for the CUL3-RING ubiquitin ligase complex (CLR3) that regulates physiological turnover of key substrates critical for maintaining vascular and renal function necessary for blood pressure control of fluid-electrolyte homeostasis.[6] Wu et al. now observed that mutated CUL3 specifically in the vascular endothelial cell reduces endothelial cell dependent vascular relaxation and NOS3 phosphorylation (S1177) that is necessary for optimal NO production. They go on to show that this is due to increased PP2A activity that is normally controlled by CUL3.

Uncovering a key role for mutated CUL3 in salt-dependent hypertension is an exciting new discovery on its own. However, a truly fascination aspect of this work is the observation that this control appears to be time of day dependent. Nocturnal hypertension and even isolated daytime hypertension increases risk of cardiovascular and renal complications.[7] Pre-clinical studies using clock-gene knockouts yield a wide range of different blood pressure phenotypes and so there is considerable complexity to the factors that regulate circadian blood pressures that may or may not be related to general hypertension or salt-sensitivity. There is evidence that CUL3 ubiquitin ligase may regulate specific clock protein turnover,[8] but this has yet to be thoroughly investigated. Most molecular studies of clock function focus on transcriptional regulation, but there have actually been a very limited number of investigations examining a wider range of physiological endpoints in more complex models. Most of what has been done is also limited to mouse models and so we know

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very little about how these mechanisms operate in a diversity of species which is an important step in translating to human relevance.

Another valuable lesson from findings with CUL3 mutants is sex specific nature of how the CLR3 system impacts acute salt handling and salt-sensitive blood pressure. In contrast to many other studies, CUL3 mutant female mice displayed a clear blunting of the natriuretic response to an acute salt load and had a greater increase in blood pressure when maintained on a high salt diet. These findings may be an important clue as to why sex differences in salt-sensitivity is not always apparent in human studies. Furthermore, other models of salt sensitivity show that males have a more severe phenotype to high salt diets and so this highlights the complexity and wider array of mechanisms that contribute to the mechanisms of sodium homeostasis.[9, 10]

On the surface, this may seem like just another study showing the importance of the endothelial NO system. While we know that loss of endothelial function is associated with a great many problems in various organ systems, the factors responsible for endothelial dysfunction can arise from a wide variety of sources. It would be very naïve for us to think that these is only one cause of endothelial dysfunction. Also, we cannot assume that endothelial dysfunction is a primary contributor to hypertension. In fact, Wu et al. shows that male CUL3 mutant mice have impaired endothelial-dependent relaxation via reduced NOS3 function, yet the blood pressure was not changed. This reinforces prior observations that loss of NO dependent relaxation is not always a predictor of hypertension risk despite what is often stated by authors.[11]

The study by Wu and colleagues demonstrates an important principle that is essential for understanding the complexities of physiological regulation and how this contributes to translational medicine. Too often the dogma is that there is one key mechanism to explain complex physiological systems which is actually rarely the case. Fortunately, these investigators recognized there may be commonalities between the renal epithelial cell and endothelial cell control systems that result in more than one phenotype (ion transport in one case and control of vascular tone in another). It is clear that there is nothing simple about the control of sodium handling despite the compulsion to simplify many conclusions from various studies into a single mechanistic pathway. Many of us can remember that our physiology courses described the control of sodium excretion into three simple areas, GFR, the renin-angiotensin-aldosterone system, and so-called "natriuretic factors" such as atrial natriuretic peptide. However, mechanisms within a wide range of cell types including various tubular epithelial cells, vascular endothelial cells, nerve cells, immune cells, and others have strong paracrine and autocrine contributions. Only by combining an array of approaches that include molecular, genetic, pharmacological and environmental methods in physiological systems will we be able to further understand complex problems such as salt-sensitive hypertension.

Disclosures

None.

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None.

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