A Natriuretic Hormone–Binding Site on the Sodium Pump

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The Na⁺,K⁺-ATPase, or “sodium pump,” is an integral membrane protein that provides an energetic underpinning to salt and nutrient reabsorption in the nephron, as well as being the central modulator of fluid and electrolyte homeostasis in humans.1,2 The exclusive basolateral localization of the sodium pump in renal (and gastrointestinal) epithelia and its functional coupling to apical sodium-dependent transport systems provide the basis for much of our understanding of renal function. The emergence of this knowledge has been a major achievement of the reductionist approach to physiologic function. The recent demonstration of a physiologic role for the ouabain-binding site in the renal response to salt challenge provides an elegant demonstration of the power of extending knowledge obtained from studies of the structure and function of single proteins to the elucidation of renal function in living organisms.

The phrase “ouabain (or digitalis) sensitive” has become a synonym for sodium pump–mediated processes, which reflects the exquisite selectivity of cardiac glycosides for this protein. Recently, this pharmacologic shorthand has taken on a fascinating and physiologically significant new dimension. It has been proposed that the highly conserved sensitivity of the sodium pump to these naturally occurring plant products mirrors the actions of endogenous circulating inhibitors of the sodium pump. These inhibitors may have an important physiologic role in pump regulation, influencing salt and water balance, and the physiologic mechanism occurs through the actions of a circulating effector of the sodium pump that acts through the ouabain-binding site. The two major findings are that mice expressing a more ouabain-sensitive sodium pump responded to a sodium load with a greater level of natriuresis than did mice expressing the wild-type isoform, and, strikingly, treatment with cardiac glycoside-sequestering antibodies equalized the natriuretic response in these mice. The most plausible explanation for these observations is that ouabain-binding characteristics of sodium pumps play a role in regulating salt and water balance, and the physiologic mechanism occurs through the actions of a circulating effector of the sodium pump that acts through the ouabain-binding site.

More than 20 years ago, de Wardener11 hypothesized the existence of a natriuretic hormone and its putative involvement in hypertension, and extensive work has been carried out to identify this natriuretic factor.12 The article by Loreaux et al.3 advances these studies using a different approach, by showing that the ouabain sensitivity of the α1 subunit and its manipulation influence renal salt handling and excretion in a way that is abolished by the presence of a reagent (the antidigitalis antibody) that removes circulating digitalis-like substances. There is a great deal of evidence that endogenous circulating cardiactonic steroid levels are higher in patients with some forms of hypertension,12–14 and it seems clear their actions are exerted through “receptor” sites on tissue sodium pumps.

The question of how cells respond to occupancy of a fraction of their sodium pumps is central to understanding the basis of many physiologic responses in which pump modulation may play a role. There are several different alternatives; these include cellular responses to changes in sodium concentrations, such as consequent changes in calcium concentra-
tions that may occur globally or locally, if a subset of sodium pumps are a part of specialized microdomains in such cells, or they may involve the postulated actions of the sodium pump as part of a signaling complex that responds to ouabain occupancy by activating intracellular signaling cascades.\textsuperscript{13} It is likely that all three mechanisms occur in a variety of physiologic situations.

It is clear today that the sodium pump, the first protein discovered as an ATP-dependent active ion transporter, whose ion pumping is central to renal function plays a more complex role in the regulation of salt and electrolyte homeostasis than previously recognized. The modulation of its actions by endogenous inhibitors has profound effects on cardiovascular and renal function. Identification of these endogenous modulators will be an exciting next step in better understanding their role in renal physiology.

DISCLOSURES

None.

REFERENCES


Appraising the Value of Genomic Association Studies

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Approaches to identify genetic determinants of disease susceptibility have evolved considerably in the past two decades. Pedigree-based linkage analysis and positional cloning strategies for finding genes responsible for Mendelian disorders caused by defects in single genes (monogenic) have now given way to a new era of genome-wide association studies (GWAS). These latter studies are designed to map loci conferring risk for more common, genetically complex diseases. Each of these approaches is fundamentally distinct, operate with contrasting assumptions, and generate results with different implications for clinical medicine.

In Mendelian disorders, rare genetic variants, usually referred to as mutations, confer a major portion of disease risk. Monogenic disorders make it feasible to construct a precise genotype–phenotype relationship and enable genetic testing to assess the probability of disease occurring in individuals and the first-degree relatives of an affected proband. Effective genetic counseling is plausible in this setting; however, monogenic mutations causing Mendelian disorders have limited value in predicting risk for disease in general populations because of the rarity of such alleles. For analysis of risk in populations, genome-wide associations are used as a probative tool based on a “common disease–common variant” hypothesis.