Is endogenous ouabain a physiological regulator of cardiovascular and renal function?

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Attempts to understand the regulation of extracellular fluid volume by the kidney and how it is linked to the pathophysiology of hypertension led to the discovery of compounds in mammalian blood and tissues that resemble cardenolides and bufodienolides (3). These so-called endogenous digitalis-like factors (EDLFS) have been the subject of intense investigation for the past 20 years, and several comprehensive reviews have been published recently (1, 2, 18). The demonstration that one circulating EDLF was either authentic plant-derived ouabain or an isomer was seminal (8). Other EDLFS have been identified, and numerous studies support the long-standing hypothesis that these factors regulate renal sodium excretion and blood pressure by a common mechanism, the inhibition of Na⁺-K⁺-ATPase. The recently discovered “signaling” effect of Na⁺-K⁺-ATPase inhibitors, which does not depend on the inhibition of the sodium pump function, provides other mechanisms by which nanomolar concentrations of EDLF might act (1, 2, 15, 18).

Despite mounting evidence, doubts about the significance of these compounds continue (9, 16). To address the questions of physiological and pathophysiological relevance, investigators have used a variety of techniques to inhibit the effect of putative EDLF. These studies have included the binding of EDLF with exogenous and endogenous antibodies (1) and the inhibition of EDLF binding by specific receptor-binding inhibitors (4, 7). Many of these experiments have been performed in hypertensive or in normal subjects exposed to physiological stress such as salt loading. Recently, a series of studies involving the genetic manipulation of the molecular structure of the α-subunits of the Na⁺-K⁺-ATPase molecule in mice have been very informative in this regard. When compared with that of wild-type mice with an ouabain-resistant α1, the response of mice with a ouabain-sensitive α1 to a salt load was enhanced but basal sodium excretion was not altered (10). Similarly, when compared with wild-type mice with a ouabain-sensitive α2, mice with an ouabain-resistant α2-enzyme were resistant to adrenocorticotropic hormone-induced hypertension but basal cardiovascular function was not altered (5, 11). These studies suggest that endogenous ouabain (EO) is more likely to be involved in pathophysiological than physiological processes.

The study reported in this issue of the American Journal of Physiology-Heart and Circulatory Physiology by Nesher et al. (14) adds to this controversy. They observed the effects of passive immunization with ouabain antibodies on blood pressure and renal sodium excretion in normal rats without physiological stressors. EO levels in normal rats were in the low nanomolar range and were reduced about 80% by a 28-day infusion of rabbit anti-ouabain antibody. This procedure had no effect on resting blood pressure but did increase aortic ring constriction reactivity to phenylephrine about 25% and increased dilator reactivity to atrial natriuretic peptide about 20%. Renal sodium excretion, measured in metabolic cages 1 day/wk during the antibody infusion, was reduced in both immunized and control rats on the second day of the infusion; it was the same as controls on remaining days, suggesting the development of a compensatory escape from the anti-natriuretic effect of immunization. Because the drop in sodium excretion occurred simultaneously with a fall in food intake of the same magnitude in both controls and antibody-infused animals (the decrease in immunized rats was significantly greater than controls), the studies were repeated in rats actively immunized against ouabain. In the study, sodium excretion measured daily for 7 days was significantly lower in immunized than control rats on 4 of the 7 days and the cumulative 7-day excretion was significantly lower by about 15%. No sign of an escape from the antinatriuresis was observed.

The study by Nesher et al. (14) provides evidence that EDLF, EO in this case, participates in the day-to-day regulation of renal sodium excretion but not blood pressure in normal animals. EO is one of two adrenal-derived EDLF currently under investigation, the other being marinobufagenin, a bufodienolide (1, 15, 18). Although both meet some of the criteria for a natriuretic hormone (NH), EO is not the ideal candidate for at least two reasons. First, salt loading in normal and hypertensive subjects appears to cause either no change or a transient increase in circulating EO levels (12, 13). Second, the α1-subunit of Na⁺-K⁺-ATPase that predominates in the kidney is ouabain resistant in rodents (17). Although EO may participate in regulating renal sodium excretion by a central mechanism (6), it is not clear that the immunization procedures used by Nesher et al. would have affected EO in the central nervous system. Nevertheless, the small changes in sodium excretion observed by Nesher et al. provide some evidence for EO being a physiological NH.

The lack of an effect of ouabain immunization on resting blood pressure is consistent with some of the studies in genetically engineered mice noted above. The demonstration that sequestration of EO in vivo reduces vascular reactivity to vasoconstrictors in vitro is consistent with the known effects of ouabain on vascular reactivity (2) and provides further evidence that circulating EO is a latent regulator of cardiovascular function with the potential for elevated levels to raise blood pressure.

The NH hypothesis has proved a fertile stimulus for much investigative work over the past 20 years, the overall result of
which is a better understanding of the sodium pump, its regulation by endogenous factors, and its potential role in integrative physiology and pathophysiology. Future studies will undoubtedly clarify many of the questions that still remain in this field.

REFERENCES