Urocortin
Advancing the Neurohumoral Hypothesis of Heart Failure
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It has now been two and a half decades since the seminal study by Vaughn and coworkers demonstrating the existence of the 41–amino acid corticotropin-releasing factor (CRF), which plays a critical role in mediating the biological responses to stress. In 2001, using sequence homology searching tools, Reyes et al identified a mouse gene encoding a 38–amino acid peptide that represented a new member of the CRF peptide family, which was termed urocortin II. The biological importance in cardiovascular regulation of urocortin II was significantly advanced in 2004 by the work of Bale and colleagues, who reported that a genetically altered mouse model deficient of the receptor to which urocortin II binds was characterized by hypertension, whereas infusion of urocortin II into cardiomyopathic mice enhanced myocardial performance. These works and those of others have provided increased momentum into basic and clinical research into this humoral system as it relates to cardiovascular disease, especially heart failure (HF).

To date, studies have established that the CRF family consists of 3 peptides (urocortins I, II, and III), which are the binding proteins for 2 G-coupled receptors, CRF-1 and -2. Although both receptors have been localized to the central nervous system, CRF-2 is most abundant outside of the brain, particularly in the heart and vasculature. Urocortin I binds to both CRF-1 and -2, whereas urocortin II and III are the ligands for CRF-2. In addition to the work of Bale et al, reports of urocortin-like immunoreactivity in the heart and the observation that infusion of urocortin I is inotropic, vasodilatory, and natriuretic in experimental HF underscore its role in the pathophysiology, diagnosis, and therapeutics of this important syndrome.3–6

The neurohumoral hypothesis of HF has taught us that circulating and local hormones participate in the complex multiorgan and cell adaptations of HF. We can now conclude that the urocortin system may be included in this hypothesis. Indeed, the work in this issue of Circulation by Rademaker et al7 advances an important role for urocortin II in HF. In this study, the investigators define for the first time the integrated cardiorenal and endocrine responses to urocortin II in a large animal model of HF produced by rapid ventricular pacing, as well as in normal animals. This model of HF has proved in the past to be a relevant paradigm of acute and chronic human HF.8,9 Using species-specific urocortin II, peptide infusion in HF enhanced cardiac output consistent with reports of a direct inotropic action of urocortin I.5 Left atrial pressure, brain natriuretic peptide, and systemic vascular resistance decreased, which is characteristic of an inodilator unloading the heart. Importantly, arginine vasopressin, aldosterone, endothelin-1, and epinephrine decreased in HF in response to urocortin II. One might conclude that in this “stressed” state, the improvement in myocardial function, and peripheral perfusion mediated this improved neurohumoral environment. Furthermore, the myocardial enhancing actions of urocortin II may also have mediated the observed improvement in renal function, although it is possible that urocortin II has direct renal actions that require further study, especially given that the kidney is known to express urocortin,10 as is discussed by the authors. The authors appropriately conclude that urocortin II has marked and beneficial hemodynamic, hormonal, and renal effects in experimental HF. They further conclude that their findings support a role for urocortin II in arterial pressure and intravascular volume homeostasis in HF, suggesting that the peptide may have therapeutic potential in this disease state. Given that the authors have reported similar actions of urocortin I in experimental and, more recently, human HF, one may conclude that both peptide hormones may have therapeutic potential.6,11

From both a biological and diagnostic perspective, it is important to question whether urocortin II is an autocrine/paracrine factor in cardiovascular regulation or an endocrine factor with diagnostic potential in the diagnosis of HF. To date, this question remains incompletely answered, although the report by Rademaker et al,7 as well as others, provides some insights. We know from previous work that urocortin is synthesized in human and mouse hearts in which urocortin mRNA has been detected, as has the protein, by immunohistochemistry.4 Importantly, Kimura et al12 in 2002 reported that urocortin mRNA could be found in all 4 chambers of the normal human heart, with the highest immunoreactivity in the left ventricle. The response of myocardial production of urocortin in the failing heart remains unclear and is an area that should be addressed in future studies. In the study in this issue of Circulation, the importance of endogenous circulating urocortin II is not discussed in detail, but one can make some observations. In normal sheep before the onset of HF, circulating values appear to be ≈18 pmol/L and increase 20% to 22 pmol/L after 7 days of HF. This is in contrast to brain natriuretic peptide, which increased 10-fold from 3 to 35.
pmol/L and which has proved to be a robust biomarker for HF, reflecting its increased myocardial production and release in this syndrome.\textsuperscript{12–14} Furthermore, because the marked increase in cardiac output with urocortin II occurred with plasma levels of urocortin II that were not markedly higher than those observed in HF, one may speculate that urocortin II functions primarily as an autocrine/paracrine factor in cardiorenal regulation. Given that Bale and coworkers\textsuperscript{3} reported hypertension in the CRF-2 receptor knockout mouse, and given the vasodilatory actions of urocortin II, it seems worthwhile to address whether urocortin II is also expressed in peripheral endothelial cells or vascular smooth muscle.

Relevant to the observation of enhanced myocardial performance in vivo with urocortin II is the very recent work this year by Ikeda and coworkers\textsuperscript{15} that urocortin II has direct myocardial cell actions beyond its inotropic properties. In this latter study, the investigators reported that urocortin II increased protein synthesis and that this action involved the CRF-2 receptor. Importantly, the protein kinase A inhibitor H89 inhibited the action of urocortin II. Thus, in vitro, urocortin II has hypertrophic actions in cardiomyocytes. The activation of the cAMP system in the heart, together with the positive inotropic action of urocortin, has important implications for its potential efficacy and safety in human HF that will need to be addressed in greater detail. Nonetheless, the study by Rademaker et al\textsuperscript{7} presents compelling findings that will need to be addressed in greater detail. Nonetheless, the study by Rademaker et al\textsuperscript{7} presents compelling findings that will need to be addressed in greater detail.


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