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 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 and decreased systemic vascular resistance. 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).

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pmol/L and which has proved to be a robust biomarker for HF, reflecting its increased myocardial production and release in this syndrome. 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 function. Given that Bale and coworkers 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 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. presents compelling findings that urocortin II is especially attractive as a peptide system, particularly in the setting of acute decompensated HF, because of its rapidly acting beneficial integrated actions to enhance cardiac output, unload the heart, augment sodium and water excretion, and suppress deleterious neurohumoral activation. Although acute intravenous administration of urocortin II would make sense in HF therapy, new technologies are emerging that could possibly make urocortin II bioavailable as an orally delivered peptide. Specifically, short, amphiphilic oligomers can be attached covalently to peptides to improve their pharmacokinetic and pharmacodynamic profile, making them orally active, as has been done recently for brain natriuretic peptide.

The use of urocortin II as part of the HF armamentarium is an exciting area for potential future research.

The action of urocortin II in the present study deserves special attention. It is clear, especially in more advanced HF, that renal impairment, which often leads to the cardiorenal syndrome, signifies a poor prognosis. Indeed, an emerging concept is that increasing renal impairment may play a role in accelerating HF owing to the renal retention of water and salt, with deleterious increases in cardiac preload and progressive cardiac pressure and volume overload. This is further complicated by the pivotal renal role in the activation of the renin-angiotensin-aldosterone system, with its vasoconstrictive and profibrotic properties. The ability of urocortin II, either directly or indirectly, to augment renal hemodynamics and enhance sodium and water excretion, together with its suppression of the water-retaining hormone arginine vasopressin and the sodium-retaining hormone aldosterone, certainly warrants further study. If such actions can be demonstrated in human HF, especially in those patients with compromised renal function, then the therapeutic value of this peptide system will be protein.

In summary, the authors of this important report provide evidence that a novel cardiovascular peptide, urocortin II, part of the CRF family of peptides, has therapeutic potential when infused into a model of experimental HF. Indirectly, their findings and those of others also suggest that this system functions more as an autocrine/paracrine factor than as a circulating endocrine system, although much more work remains to be done. Clearly, continued investigation into the role of the urocortins in the pathophysiology, diagnosis, and therapeutics of evolving HF should be encouraged. The next decade of research into these areas will be exciting.

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Disclosures

None.

References


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