Exploring new drugs for heart failure: the case of urocortin

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This editorial refers to 'Urocortin 2 infusion in human heart failure' by M.E. Davis et al., on page 2589

Over the past decade, clinical development of natriuretic peptide analogues as drug therapy for acute heart failure has sparked a wide range of interests to seek other endogenous vasoactive peptide systems that are operative as adaptive responders in human heart failure. With rapid advances in the molecular understanding of heart failure pathogenesis, several novel neurohormonal systems have been identified and more are under study. Bringing a potential therapeutic concept from bench to bedside today often involves a prerequisite set of animal and human studies. However, much of the attention in recent years has focused on identifying what the best clinical end-points should be or what the sample size should be in order to power statistical significance. Sometimes the fundamental mechanisms of action are overlooked with the rush to clinical implications. Opportunities to refine our thinking in the exploitation of such neurohormonal agonists/antagonists can be easily missed.

Davis and colleagues have extended our understanding of a new neurohormone and its pathophysiological role in heart failure1. Urocortin is actually a group of peptides belonging to the corticotrophin-releasing factor (CRF) family, with other members including urocortin 1, urocortin 2, and urocortin 3. It is interesting to point out that the urocortin system has been conserved throughout evolution in vertebrates all the way back to the amphibian sauvagine.2 It is interesting to point out that the urocortins act on specific G-protein-coupled receptors that subserve important adaptive responses to protect the heart and circulation, thus ensuring survival. The urocortins act on specific G-protein-coupled receptors that subserve important adaptive roles. This system appears to release corticosteroids in response to stress, at the same time contributing to some 'cardioprotective' properties. Other neurohormones such as angiotensin II, arginine vasopressin, natriuretic peptide and norepinephrine similarly share >600 million years of history and serve important adaptive responses to protect the heart and circulation, thus ensuring survival. The urocortins act on specific G-protein-coupled receptors that subserve important homeostatic physiological functions: urocortin 1 acts on both CRF1 receptors in the central nervous system and CRF2 receptors in the myocardium, whereas urocortin 2 and urocortin 3 act selectively for specific CRF2 receptors found in the myocardium and arteriolar vessels. CRF2-deficient mice demonstrate elevated blood pressure.3 Reports to date suggest that urocortin has a complex role in volume and pressure homeostasis. Based on existing data, these peptides are still considered primarily as vasodilators. Neurohormones such as urocortin stabilize haemodynamic alterations in heart failure and hypertension, and are attractive pathways to drug development. However, there are several fundamental gaps that have to be filled.

First and foremost, is there a direct association between the neurohormonal system and the disease state? Identification of CRF2 receptors in the myocardium and certain blood vessels provides the first evidence of their involvement in cardiac diseases, with urocortin 2 and urocortin 3 expression abundant in the myocardium.2 In animal experiments, the expression of endogenous cardiac urocortin is increased in response to ischaemia–reperfusion damage, and the addition of exogenous urocortin is associated with reduction of myocardial cell death during ischaemia–reperfusion damage.4 Furthermore, gene expression of urocortin has been demonstrated in human myocytes derived from both dilated and hypertrophic cardiomyopathy,4 and elevated levels of circulating urocortin can be found in patients with heart failure. Taken together, the role of urocortin in heart failure pathophysiology appears convincing.

Secondly, does modification of an observed pathophysiological mechanism directly relate to improvement in disease? If improvement is determined by resolution of haemodynamic alterations, the answer is affirmative. The group from Christchurch in particular has systematically studied all three urocortin infusions in normal and experimental heart failure animal models, normal humans, and now humans with heart failure. Consistently, they all produce substantial and prolonged cardiac vasodilatory and inotropic effects,5–8 and the reverse effects were seen when receptors were competitively antagonized.9 However, short-term administration of urocortin 1 did not show any significant haemodynamic or neurohormonal effects either in normal subjects or in patients with heart failure.10,11 In contrast to the report of Davis and colleagues1, short-term urocortin 2 infusion caused flushing in all eight male patients with stable heart failure, consistent with its vasodilatory
properties. Overall, cardiac output improved with urocortin 2 infusion in the setting of an increase in heart rate and decrease in blood pressure, while estimated cardiac work was decreased. All changes were observed to occur in a dose-dependent manner. In addition, several neurohormones, including plasma renin activity, angiotensin II, arginine vasopressin, aldosterone, and norepinephrine, were largely unchanged. There is, therefore, modification of a mechanism, but we do not yet know if the disease process is favourably affected.

Thirdly, does the intended therapeutic intervention have incremental benefit over existing therapies? From the report of Davis and colleagues, there are several unanswered questions regarding the potential risks of urocortin 2 infusion. For example, the lack of effect on neurohormones is somewhat surprising, given the marked suppression seen in experimental heart failure. Although natriuretic peptide levels were unchanged with urocortin 2 infusion in normal humans, plasma natriuretic peptide levels were augmented in the setting of haemodynamic improvement with urocortin 2 infusion. The implications of this finding are not clear, but activation of the CRF2 receptor with urocortin can induce the production of atrial and B-type natriuretic peptide in cultured neonatal rat cardiomyocytes, at least in part via the cAMP-dependent protein kinase A pathway during cardiac hypertrophy. In contrast, long-term infusion of urocortin 1 in animal models can result in late reduction of natriuretic peptide levels, and short-term human infusion did not lead to any significant changes.

Hence, the observed surge in plasma natriuretic peptide levels needs to be confirmed and the underlying mechanisms further explored. Another observation unique to urocortin 2 infusion is the noticeable increase in heart rate with urocortin 2 infusion in animal models, and in patients with a failing heart. This was not observed with urocortin 1 infusions, and therefore begs the question as to whether long-term effects of urocortin 2 may interact with the autonomic system and be potentially detrimental. Furthermore, the observed increase in serum creatinine in the combined analysis of the urocortin 2-treated group vs. the controls coupled with the relatively lower urine output is not reassuring, and is consistent with a previous report on urocortin 2 infusion in normal humans. Taken together, the safety profile of this therapeutic approach remains to be verified.

The lack of internal consistency between animal and human data suggests that the fundamental understanding of urocortins and their receptors in the pathophysiology of heart failure is incomplete. The bigger question is at what stage of heart failure is urocortin 2 likely to be most beneficial. Our view is that it may be more likely to benefit patients in the earlier stages. There are recent reports suggesting that urocortin may have a greater impact in attenuation of disease progression during the earlier stages of experimental heart failure than late salvage of compensated states. While Davis and colleagues have given urocortin 2 as a short-term infusion to demonstrate its vaso-dilatory effects, the peptide should not be pigeon-holed as a therapy only useful in the acute stages. Elegant studies such as this, coupled with a wide range of molecular and physiological investigations, will probably provide greater insight.

Conflict of interest: G.S.F. and W.H.W.T. have previously served as paid consultants to Neurocrine Biosciences Inc.

References