Letter Regarding Article by Rademaker et al, “Integrated Hemodynamic, Hormonal, and Renal Actions of Urocortin 2 in Normal and Paced Sheep: Beneficial Effects in Heart Failure”

To the Editor:

I read with great interest the study by Rademaker et al1 reporting the beneficial cardiovascular and humoral effects of urocortin 2 in sheep with heart failure induced by pacing. Urocortin 2 is a potent vasodilator peptide that acts specifically on the corticotropin-releasing factor type 2 receptor. The study by Rademaker et al1 suggests that this peptide may have therapeutic potential in patients with heart failure. However, I would like to remind the readers that the presence of urocortin 2 peptide in human tissues, including the heart, has not been established so far. If human urocortin 2 is not an endogenous peptide, the administration of the authentic peptide may cause allergic responses in human subjects.

The complementary DNA coding urocortin 2 was shown to be present in humans, but the predicted human urocortin 2 precursor lacks a consensus proteolytic cleavage site that would allow C-terminal processing of the peptide.2,3 Initially, it had been referred to as a urocortin-related peptide sequence. Furthermore, no reports are available on the presence of immunoreactive urocortin 2 in human tissues shown by either radioimmunoassay or immunohistochemistry. In contrast, our previous studies have shown the presence of urocortin 1 and urocortin 3 in human heart and other human tissues by means of radioimmunoassay and immunohistochemistry.4,5

The important issue before the clinical use of this peptide is therefore to clarify whether or not urocortin 2 is an endogenous peptide in humans. This issue could be clarified by studies using radioimmunoassay and immunohistochemistry if a specific urocortin 2 antibody is available. Another important issue would be to clarify whether urocortin 3, another specific agonist for corticotropin-releasing factor type 2 receptor, has potent effects on heart failure similar to those found in urocortin 2.1

Disclosures

None.

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Response

We thank Dr Takahashi for his interest in our article.1 He expresses concern that because there are currently no reports available on the presence of urocortin 2 (Ucn2) immunoreactivity in human tissues, the peptide may not be an endogenous factor in humans and thus administration may cause an allergic response. However, although the Ucn2 protein has yet to be demonstrated in human tissue (or plasma), positive immunostaining for human Ucn2 in several human neuronal cell lines2 and expression of Ucn2 gene transcripts in multiple human organs and tissues (including the heart)3 strongly suggest that it is an endogenous peptide in humans. Although immunologic detection of Ucn2 in human tissue would certainly help to clarify this issue, it is highly unlikely that Ucn2 mRNA is expressed in human tissues but not translated to the Ucn2 protein, particularly in light of the fact that humans express both mRNA and peptides for Ucn1 and Ucn3.

Importantly, our group has recently completed an investigation on the effects of human Ucn2 administration in normal human subjects (25 μg and 100 μg infused over 1 hour on separate days, 2 to 5 weeks apart).4 We found that infusion of Ucn2 induced significant and dose-dependent hemodynamic effects, including marked increases in cardiac output and reductions in systemic vascular resistance and diastolic blood pressure, with no evidence of any adverse effects or allergic reactions. These findings provide further evidence that Ucn2 is an endogenous protein in humans, and clear the way for clinical investigation of the peptide in human disease.

In regard to Dr Takahashi’s query concerning the actions of Ucn3 in heart failure, we have recently concluded a study on the effects of Ucn3 in our ovine model of congestive heart failure, the results of which are pending publication.

Disclosures

None.

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