Ang-(1-7) and vascular function - the clinical context

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It is now well established that the renin angiotensin system (RAS) comprises two axes, 1) the classical axis comprising angiotensin converting enzyme (ACE)-angiotensin II (Ang II)-Ang II type 1 receptor (AT_1R) and 2) the recently characterised ACE2-angiotensin-(1-7)-Mitochondrial Assembly Receptor (MasR) axis (1,2) (figure). Physiologically, both systems likely play a coordinated role in regulating cardiovascular function. Hyperactivation of the ACE-Ang II-AT_1R axis generally causes deleterious effects, such as vasoconstriction, endothelial dysfunction, inflammation, fibrosis, thrombosis, angiogenesis and is pro-hypertensive, whereas activation of the ACE2-Ang-(1-7)-MasR axis of the RAS opposes effects of the classical system and accordingly has been described as the protective arm of the RAS (2). Recent evidence indicates that Ang-(1-7) also mediates part of its cardioprotective effects by acting as an endogenous β-arrestin-biased agonist at the AT_1R (3). In addition to MasR, it has been suggested that Ang-(1-7) binds Mas-related G proteins, such as MyrD (Mas-related G protein-coupled receptor D) (4). However whether this is functionally significant remains to be confirmed, especially in humans.

Ang-(1-7) induces vasodilatory, anti-inflammatory, anti-fibrotic, anti-angiogenic and anti-hypertensive effects by binding to its G-protein coupled MasR. Ang-(1-7) also improves glucose and lipid homeostasis (2). These actions of Ang-(1-7) make this heptapeptide an attractive target for cardioprotective therapies and beneficial effects of Ang-(1-7) have been demonstrated in numerous animal models of human disease, including hypertension, heart failure, stroke, obesity, diabetes, atherosclerosis, renal disease and aortic aneurysm (2). In experimental models of diabetes, Ang-(1-7) ameliorates cardiac and renal dysfunction (2,5). Moreover, Ang-(1-7) has been considered a novel anti-cancer treatment through its anti-angiogenic functions (6).

Almost all studies showing cardiovascular protective effects of Ang-(1-7) have been conducted in animal models, with very few clinical studies demonstrating therapeutic potential.

In particular, while Ang-(1-7) has been shown to have potent vasodilatory effects in many vascular beds in rodents, there is a paucity of information in humans and the few data that are available are conflicting. Some studies demonstrated that intra-arterial infusion of Ang-(1-7) increases forearm blood flow in healthy subjects with blunted responses in hypertensive patients (7), while others failed to demonstrate any vasodilatory effect of intra-brachial Ang-(1-7) infusion in humans (8). In human atrial and adipose microvessels, Ang-(1-7) induces vasodilation via nitric oxide (NO)- and telomerase-dependent processes through MasR, effects that are absent in patients with coronary artery disease (9). The relatively small number of clinical studies has not shown convincing evidence for a vasoprotective effect of Ang-(1-7) and may relate, at least in part, to sub-optimal dosing, instability of the peptide, and heterogeneous patient groups.

In the current issue of the journal, Schinzari et al (10) further explored the vasodilatory role of Ang-(1-7) in the context of obesity-associated vascular dysfunction. They demonstrated that in obese patients intra-arterial infusion of Ang-(1-7) increased forearm blood flow, amplified acetylcholine-induced vasodilation in the presence of insulin, and attenuated endothelin-1-induced vasoconstriction. However, unlike previous human and experimental studies, these responses were not blocked by the MasR antagonist, A779, indicating Mas-independent vasodilatory signalling by Ang-(1-7). In this context, it may be speculated that Ang-(1-7) mediates effects through alternative receptors, such as the AT_2R, since Ang-(1-7) has been shown, at least experimentally, to signal through AT_2R (figure). Perhaps future clinical studies might address this by exploring Ang-(1-7) vascular effects in the presence of an ACE2 inhibitor. It should also be recognised, that although A779 did not block Ang-(1-7) vascular effects in obesity, the authors did not actually demonstrate MasR blockade, and hence it remains uncertain whether A779, at the dose used and in the experimental conditions, truly

inhibited MasR activation. Accordingly, some caution should be exercised when attributing vascular Ang-(1-7) effects to MasR-independent processes in obesity.

While the study of Schinzari (10) and others (7,9) strongly suggest a vasoprotective effects of Ang-1-7 in humans with it being a promising candidate in the treatment of cardiovascular disease, the question that arises is why have there not been more clinical trials to test the therapeutic potential of Ang-1-7 in human disease and particularly in cardiovascular pathologies? In fact there are only a few registered clinical trials on ClinicalTrials.org for Ang-(1-7) and none of these have yet started for cardiovascular disease. Reasons for the slow progress in translating Ang-(1-7) as a therapy from the pre-clinical setting to the clinic may relate to challenges in developing a stable peptide and to limitations regarding unfavourable pharmacokinetic properties. Ang-(1-7) is a peptide with a short half-life and low bioavailability due to the rapid enzymatic metabolism by peptidases including ACE and dipeptidyl peptidase 3 (DPP 3) (1,9). Also, the peptide is rapidly degraded in the gastrointestinal tract when administered orally. It has been suggested that improved drug exposure could be attained by coadministration of Ang-(1-7) together with an ACE inhibitor, which prevents Ang-(1-7) degradation. Ang-(1-7) analogues and different preparations that have been developed for clinical use include NorLeu^{3}-Ang-(1-7), (DSC127, as a topical preparation) HPβCD/Ang 1-7, AVE-0991, cyclic Ang-(1-7), CGEN-856 and TXA127 (11). Another potential approach to increase endogenous Ang-(1-7) levels, is by increasing ACE2, which converts Ang II to Ang-(1-7). Small clinical studies using recombinant ACE2 in acute respiratory distress syndrome have already shown potential benefit (12).

Of the Ang-(1-7) analogues, DSC127 is currently in a phase III clinical trial testing the safety and efficacy of topical application in accelerating the healing of diabetic foot ulcers (13). Another Ang-(1-7) analogue, TXA127, is being used in patients with Duchenne muscular dystrophy or congenital muscular dystrophy (11). There has also been some interest in using

Ang-(1-7) as an anti-angiogenic agent in cancer and pharmacokinetic studies have been completed to test safety (7). Patients with metastatic sarcoma were treated with Ang-(1-7) administered by subcutaneous injection, and while the cancer biomarker endpoints were not achieved, some patients had prolonged disease stabilization. Although there are no current trials to assess Ang1-7 effects on blood pressure, a study has been registered on ClinicalTrials.org to investigate the acute effects of the peptide on blood pressure and heart rate in healthy and hypertensive patients. Findings from this clinical study should provide important direction regarding Ang-(1-7) as a potential cardiovascular protective therapeutic agent in clinical medicine.

The study under discussion in this issue of the journal (10) not only supports the concept of activating the protective arm of the RAS by Ang-(1-7) treatment, but it also highlights the fact that obese patients with vascular dysfunction may benefit from such a therapeutic approach. Whether this is true will only be elucidated in future large clinical trials. With the ongoing development of new Ang-(1-7) analogues and human studies such as that described by Schinzari et al (10), the time is now ripe to advance the field in the alternative RAS pathway (ACE2-Ang-(1-7)-MasR) to the clinical arena so that the strong pre-clinical data on the cardiovascular benefits of Ang-(1-7) can be translated to the patient.

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Figure legend

Diagram demonstrating the two axes of the renin angiotensin system, and the receptors through which Ang-(1-7) signals in human vessels. In obesity, it seems that Ang-(1-7) signals through MasR-independent pathways, possibly involving AT_2R, as indicated by the hatched line in the figure.