A Novel Mechanism of Action for Angiotensin-(1–7) via the Angiotensin Type 1 Receptor

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Angiotensin-(1–7) (Ang-[1–7]) was originally thought to be an inactive metabolite of Ang II in the renin–angiotensin system (RAS). However, reported biological effects and seminal discoveries of an angiotensin-converting enzyme (ACE) homolog, ACE2 that metabolises Ang II to Ang-(1–7),[1] combined with identification of the G-protein–coupled receptor Mas as an endogenous Ang-(1–7) receptor[2] defined a natural counter-regulatory ACE2/Ang-(1–7)/Mas axis of the RAS. The counter-regulatory axis of the RAS is firmly established to inhibit detrimental effects mediated through the classical ACE/Ang II/angiotensin type 1 receptor (AT_1R) axis (Figure). Moreover, it is simplistic to separate the RAS into these 2 axes because the systemic and local tissue-specific RAS includes a wide range of molecules with biological action, including the alternative Ang II receptor, the angiotensin type 2 receptor (AT_2R), other peptide metabolites, for example, Ang-(1–9), Ang III, and Ang IV, and recent discoveries including an Ang-(1–7) metabolite, alamandine, and its receptor Mas-related G-protein–coupled receptor D.[3]

Ang-(1–7) mediates varied physiological and therapeutic effects via Mas, including preventing adverse tissue remodeling, improving vascular and cardiac function, and promoting wound healing. Importantly, effects of Ang-(1–7) are not all directly through antagonizing the ACE/Ang II/AT_1R axis. In fact, Ang-(1–7), through Mas and $G_{\alpha s}$,[4] activates distinct intracellular signaling leading to production of nitric oxide, modulation of ERK signaling, and stimulation of cAMP release.[5] Therefore, Ang-(1–7) is well established as an independent RAS component and is being explored clinically, for example, for stimulating hematopoietic recovery in patients with cancer after chemotherapy.[6]

In this issue of *Hypertension*, the complexity of RAS interactions, and particularly Ang-(1–7) function, is further expanded by Galandrin et al,[7] via a series of elegant molecular pharmacology studies that decipher a novel role for Ang-(1–7) as a biased AT_1R agonist[7] (Figure) and, therefore, define a previously unrecognized mechanism of action. The concept of biased agonism at the AT_1R is relatively new and stems from the recognition that biased AT_1R agonists, for example, the peptide [Sar1, Ile4, Ile8]-Ang II, stimulate β-arrestin recruitment to the receptor leading to AT_1R internalization, β-arrestin–dependent signaling and potential therapeutic outcomes, which are distinct to the classical G-protein–coupled responses.[8] Galandrin et al[7] performed a systematic evaluation of angiotensin peptides in AT_1R-overexpressing HEK293T cells. Bioluminescence resonance energy transfer was used to assess abilities of Ang II, Ang III, Ang IV, and Ang-(1–7) to activate classical G_α signaling. Although Ang III and Ang IV mimicked Ang II in activating G_α signaling via $G_{\alpha i/o}$, $G_{\alpha q/11}$ and $G_{\alpha 13}$ families, Ang-(1–7) did not. Binding affinity studies revealed all angiotensin peptides displaced ^{125}I-Ang II from the AT_1R, with affinities from nmol/L (Ang II and Ang III) to μmol/L (Ang IV). Ang-(1–7) was reported to have a Ki of 360 nmol/L and act as a natural neutral antagonist at the AT_1R by shifting the Ang II response curve to the right for the activation of $G_{\alpha i3}$ and, with lower potency, $G_{\alpha q}$. Importantly, Ang-(1–7) also acted as a biased AT_1R agonist by stimulating β-arrestin2 recruitment. The potency of Ang-(1–7) was lower than Ang II, but in line with its binding affinity and inhibited by the AT_1R blocker candesartan.

Biased AT_1R agonism is being actively investigated for therapeutic applications. The classical actions of Ang II at the AT_1R in hypertension and cardiovascular disease are mainly mediated through activating $G_{\alpha q}$. Conversely, AT_1R signaling also leads to non–G-protein–mediated signaling through β-arrestin2, which is therapeutic in cardiovascular disease. Currently, the β-arrestin2–biased AT_1R molecule TRV1200027 is being explored in clinical trials for heart failure after demonstrating efficacy in reducing blood pressure and improving cardiac function in rodent models.[9] The therapeutic development of biased AT_1R agonists is important in the context of Ang-(1–7) as a biased AT_1R agonist. Galandrin et al[7] moved from in vitro molecular pharmacology studies to a whole-organ model in isolated aortas from wild-type and AT_1R knockout mice. Ang-(1–7) inhibited phenylephrine-induced contraction[7] in wild-type, but not AT_1R knockout aortas. Moreover, effects of Ang-(1–7) in wild-type aorta were not inhibited by the Mas antagonist A-779, nor the AT_2R antagonist PD-123,319, but were by candesartan. Intriguingly, when Ang II was used as a vasoconstrictor in aortas from wild-type mice, coapplication of Ang-(1–7) potentiated the effect in a manner sensitive to the Mas antagonist A-779. The reason for this finding is not clear but highlights the complexity of RAS interactions. Previous studies have highlighted cross talk between Ang-(1–7) and other RAS receptors, with effects reported via the AT_2R[10] and Mas-related G-protein–coupled receptor D.[4] However,

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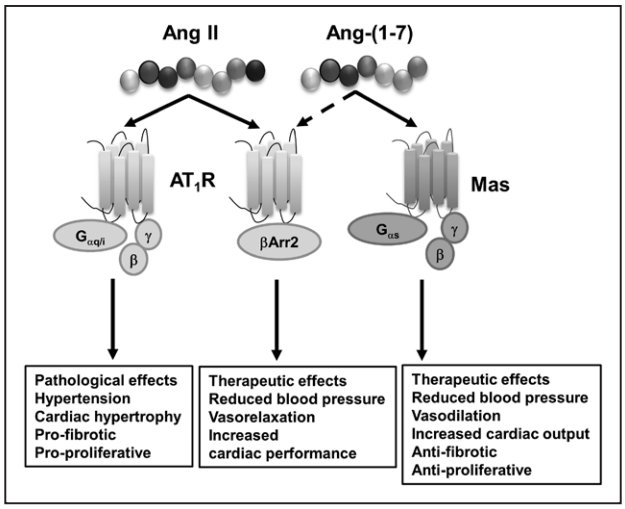

Figure. New model of angiotensin-(1–7) (Ang-[1–7]) action. Ang II acts at the angiotensin type 1 receptor (AT_1R) and stimulates (patho)physiological G-protein signaling in cardiovascular disease, mainly through the $G_{\alpha q/i}$ family. Ang II also activates G-protein–independent signaling via recruitment of β-arrestin2 (βArr2) leading to therapeutic effects. The counter-regulatory renin–angiotensin system axis peptide Ang-(1–7) mainly acts at Mas to stimulate diverse therapeutic effects in different diseases via $G_{\alpha s}$ activation. Ang-(1–7) also binds the AT_1R leading to βArr2 recruitment and vasorelaxation in isolated aortas.

AT_2R studies have predominantly used the AT_2R antagonist PD-123,319, which is also reported to inhibit Mas-related G-protein–coupled receptor D that may complicate interpretation.[3,4] Furthermore, Mas is also a physiological antagonist of the AT_1R, again highlighting the complexity of cross talk in the RAS.[11] These new studies[7] are the first demonstration that Ang-(1–7) can both interact with the AT_1R and mediate distinct signaling effects and provide new knowledge about how RAS components interact via cross talk.

What remains to be dissected is how these individual peptide/receptor interactions function in vivo. In a diseased tissue, there are likely to be differing levels of RAS-related receptors and dynamically changing angiotensin peptide levels, and it will be difficult to determine the relative contribution of individual peptides acting at different receptors. Nevertheless, it will be important to research the contribution of biased agonism from Ang-(1–7) at the AT_1R and integrate the knowledge with that known through Mas agonism.

In summary, this study[7] has defined novel interactions in the RAS and contributes to increased knowledge of how RAS peptides and receptors intersect to mediate biological outcomes. Further understanding of these aspects of the RAS may lead to the next generation of RAS-targeting medicines capable of integrating differential signaling outcomes into synergistic action in cardiovascular disease.

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Disclosures

None.

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