ACE2/Ang (1-7)/MasR axis during AT1R blockade, with studies have highlighted the potential importance of the occurs during administration of these agents. Preclinical blockers could be attributed to elevated Ang (1-7) levels that Ang (1-7).3 Thus, manipulation of this axis has become the (1-7)/MasR axis, with deficiency in ACE2 increasing both expression or activity of components of the ACE2/Ang mediated by Ang II may in part be attributed to reduced antioxidative metabolite Ang (1-7). Research over the last decade supports the hypothesis that the deleterious effects of Ang II. With the identification and cloning of the ACE homologue ACE2 and the discovery of the G protein–coupled Mas receptor (MasR) as an Ang (1-7) binding site, the ACE2/Ang (1-7)/MasR axis is considered to counterbalance the ACE/Ang II/AT1R axis. Evidence of protective effects mediated by Ang (1-7) has highlighted the importance of ACE2 in regulating Ang (1-7) levels, with local activity of ACE2 determining the relative levels of the vasoconstrictor and pro-oxidative peptide Ang II and its vasodilator and antioxi
dative metabolite Ang (1-7).7 Research over the last decade supports the hypothesis that the deleterious effects mediated by Ang II may in part be attributed to reduced expression or activity of components of the ACE2/Ang (1-7)/MasR axis, with deficiency in ACE2 increasing both tissue and circulating levels of Ang II while reducing levels of Ang (1-7).3 Thus, manipulation of this axis has become the focus of recent studies to determine whether a therapeutic benefit may prevail.

It is well recognized that ACE inhibitors increase plasma Ang (1-7) levels.4 Emerging evidence also suggests that at least part of the benefits observed with the use of AT1R blockers could be attributed to elevated Ang (1-7) levels that occur during administration of these agents. Preclinical studies have highlighted the potential importance of the ACE2/Ang (1-7)/MasR axis during AT1R blockade, with increased ACE2 activity leading to increased Ang (1-7) production, complemented by similar findings reported in patients after treatment with the AT1R antagonist irbesartan.6 In the current issue of Hypertension, Iwai et al7 present more supportive data for a possible involvement of the ACE2/Ang (1-7)/MasR axis in the actions mediated by the AT1R antagonist olmesartan in the context of vascular remodeling. Using the femoral artery cuff model in mice, they reported that this inflammatory model of vascular injury markedly reduced ACE2 and MasR expression but did not alter ACE levels. Previous studies have also reported decreased expression/activity of components of this axis; however, there is still controversy as to whether downregulation of the ACE2/Ang (1-7)/MasR axis contributes to cardiovascular pathology, because increases in expression of various components of the ACE2/Ang (1-7)/MasR axis in cardiovascular disease have also been reported.1,3 What was interesting was the finding that chronic Ang (1-7) infusion, started at the same time as placement of the femoral cuff, significantly attenuated neointimal development despite the apparent low MasR expression in the injured vessels.7 Although the authors speculate that Ang (1-7) may mediate vasoprotection at the beginning of the treatment period before a marked reduction in MasR occurs, it is difficult to reconcile this anomaly until studies examining the time course of MasR expression in this model are performed. Iwai et al7 confirmed that the reduction in neointimal formation occurred via action of Ang (1-7) at the MasR, because this effect was abolished with coadministration of the Ang (1-7) antagonist [D-Ala(7)]-Ang (1-7), also known as A-779. The fact that A-779 itself increased neointimal formation supports a tonic inhibitory role for the ACE2/Ang (1-7)/MasR axis in vascular remodeling after cuff placement, consistent with ACE2-deficient mice exhibiting both increased cuff-induced neointima (current study) and increased early vascular inflammation.8 In agreement with these studies, chronic Ang (1-7) treatment decreased atherosclerotic lesion progression and reduced in-stent restenosis and neointimal formation after vascular injury.9,10 Iwai et al7 further report decreased neointimal formation with chronic olmesartan treatment and showed a partial reversal of this effect when cotreated with the MasR antagonist A-779, consistent with other studies showing partial reversal by A-779 of sartan-evoked cardiac remodeling.5 The authors of the current study speculate that the partial involvement of Ang (1-7) in the beneficial effect of AT1R blockade can be attributed to either low levels of ACE2 and MasR expression after injury or that the modulation by Ang (1-7) is simply complementary to a predominant effect of AT1R blockade to inhibit neointimal formation.

Ganging up on Angiotensin II Type 1 Receptors in Vascular Remodeling

Tracey A. Gaspari, Antony Vinh, Emma S. Jones, Robert E. Widdop

See related article, pp 137–144

In recent years there has been a revolution in our knowledge of the renin-angiotensin (Ang) system (RAS), with the identification of novel functions for biologically active Ang peptides and receptors and the discovery of new enzymes, such as Ang-converting enzyme (ACE) 2 within the RAS.1,2 The discovery that Ang (1-7) promotes vasodilation, antiproliferative, antifibrotic, antiatherosclerotic, and anti-inflammatory effects that oppose those mediated by Ang II acting at the Ang type 1 receptor (AT1R) has contributed to the identification of 2 opposing axes within the RAS (see Figure). The original pathway of the RAS involving Ang II/ACE/AT1R that mediates pressor and volume homeostasis is also responsible for the majority of pathogenic effects of Ang II. With the identification and cloning of the ACE homologue ACE2 and the discovery of the G protein–coupled Mas receptor (MasR) as an Ang (1-7) binding site, the ACE2/Ang (1-7)/MasR axis is considered to counterbalance the ACE/Ang II/AT1R axis. Evidence of protective effects mediated by Ang (1-7) has highlighted the importance of ACE2 in regulating Ang (1-7) levels, with local activity of ACE2 determining the relative levels of the vasoconstrictor and pro-oxidative peptide Ang II and its vasodilator and antioxidative metabolite Ang (1-7).7 Research over the last decade supports the hypothesis that the deleterious effects mediated by Ang II may in part be attributed to reduced expression or activity of components of the ACE2/Ang (1-7)/MasR axis, with deficiency in ACE2 increasing both tissue and circulating levels of Ang II while reducing levels of Ang (1-7).3 Thus, manipulation of this axis has become the focus of recent studies to determine whether a therapeutic benefit may prevail.

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There is another possibility offered by the authors, that of Ang II type 2 receptor (AT₂R) involvement, which was not explored in the current study. In fact, the same group have reported previously that AT₂R stimulation was involved in the inhibitory effect of valsartan on vascular remodeling, because of increased Ang II levels acting at unopposed AT₁R. Ang (1-7) can act via both the MasR and the AT₂R, as seen in the apolipoprotein E⁻/⁻ mouse model of atherosclerosis, where both vasoprotective and atheroprotective effects mediated by Ang (1-7) could be abolished by either A-779 or the AT₂R antagonist PD123319. Furthermore, Ang (1-7)–mediated vasodepressor effects can occur exclusively via stimulation of AT₂R in adult normotensive rats, whereas both AT₁R and MasR are involved in the Ang (1-7)–mediated vasodepressor response in aged rats. Like the MasR, activation of the AT₂R generally produces effects that oppose those mediated by the AT₁R. AT₂R expression is upregulated in many disease states, such as hypertension, vascular injury, atherosclerosis, myocardial infarction, heart failure, renal failure, and cerebral ischemia, indicating a potential role for this receptor in cardiovascular disease. Interestingly, in an earlier study conducted by the same group, AT₁R expression was increased in the injured femoral artery after cuff placement, which would distinguish AT₂R plasticity from that of MasR (decreased in current study) in the cuff model, although both subtypes were not examined concomitantly in the same study.

The observations of Iwai et al. strengthen the hypothesis that beneficial actions of AT₁R blockers may involve activation of the ACE2/Ang (1-7)/MasR axis, but they may also indirectly link with the counterregulatory effects of the AT₂R arm. In the absence of Ang peptide measurements in the current study, it is tempting to speculate that increased ACE2 activity caused by AT₂R blockade results in elevated Ang (1-7) levels that may act not only on MasR (ie, A-779–sensitive) but also on (upregulated) AT₂R and so contribute to olmesartan-induced antiremodeling of the injured artery (see Figure).

It is evident that there has been substantial progress made in the last few years that indicates that this vasoprotective axis of the RAS has therapeutic potential for treating cardiovascular disease. However, there are many issues that still need to be addressed on this journey, including cross-talk between the AT₁R and MasR, the role of AT₂R in effects mediated by the ACE2/Ang (1-7)/MasR axis, distinguishing MasR and AT₂R signaling pathways, and targeting the ACE2/Ang (1-7)/MasR axis at a tissue/cellular level. One thing appears clear, restoration of the balance between the ACE/Ang II/AT₁R axis and the ACE2/Ang (1-7)/MasR axis should lead to improved outcomes against cardiovascular disease.

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Disclosures

None.

References


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