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COMMENTARY

Role of the ACE2/angiotensin1–7/Mas axis in the cardiovascular system

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Angiotensin (Ang) 1–7 is a new bioactive product in the renin–angiotensin system. Most studies on the actions of Ang1–7 were started after the synthesizing enzyme ACE2 (angiotensin-converting enzyme 2) and the receptor Mas were discovered.[1,2] Ang1–7 is produced by the protease activity of ACE2 as a derivative of Ang I and Ang II. Ang1–7 together with ACE2 and Mas form a separate pathway in renin–angiotensin system called the ACE2/Ang1–7/Mas axis. Previous reports indicate that Ang1–7 induces vasodilatation, anti-inflammatory responses and anti-cell growth effects.[3] These results suggest that Ang1–7 functions as an inhibitor or modulator of the angiotensin II receptor (AT_1 receptor)-mediated responses caused by classical Ang II. Ang1–7 seems to function mainly as a local mediator, but it may also function as a circulating hormone.[4] The balance between the classical ACE/Ang II/AT_1 receptor axis and the ACE2/Ang1–7/Mas axis has an important role in the exacervation and prevention of cardiovascular disorders. An ACE2 deficiency induced renal damage and cardiac dysfunction in animal models.[5,6]

A recent report indicated that an AT_1 receptor blocker (ARB), such as olmesartan increases the actions of the ACE2/Ang1–7/Mas axis.[7] A study by Hayashi *et al.*[8] in an article appearing in this issue of *Hypertension Research* also suggests the involvement of the ACE2/Ang1–7/Mas axs in the inhibitory effects of olmesartan on AngII-mediated responses in vascular cells. They showed that an Ang II-mediated increase in the phosphorylation of the extracellular signal-regulated kinase (ERK) 1/2 in vascular smooth muscle cells was reduced by olmesartan. This inhibition by olmesartan was attenuated by treatment with the Ang1–7 antagonist D-Ala7-Ang1–7. Similar changes were observed in the cell proliferation and ERK1/2 phosphorylation of human umbilical vein endothelial cells and the adhesion of monocytes to human umbilical vein endothelial cells. The inhibitory action of Ang1–7 on ERK1/2 activity was also reported in proximal tubular cells of the kidney.[9] However, in some cases, Ang1–7 is reported to activate mitogen-activated protein kinase in human mesangial tissue[10] or enhance the Ang II-mediated increase in ERK1/2 phosphorylation in mouse bone marrow-derived dendritic cells.[11] These results suggest that the role of Ang1–7 in the activation of ERK1/2 or mitogen-activated protein kinase is still controversial and depends on conditions, such as cell type and dosage. Moreover, Giani *et al.* also reported that Ang1–7 displays dual action to stimulate either the Mas or AT_1 receptor or both.[12] They observed that Ang1–7 stimulated STAT3 and STAT5a/b phosphorylation through the AT_1 receptor and attenuated Ang II-stimulated ERK1/2 and Rho kinase phosphorylation through Mas receptor activation.[12] The authors concluded that the latter effect of Ang1–7 could be a protective effect against locally generated Ang II in the heart. This result suggests a possible therapeutic role for Ang1–7 in cardiac injury; however, proper conditions are necessary for Ang1–7 to elicit its protective effect on the heart.

One of the important features of the ACE2/Ang1–7/Mas axis is its interaction with classical AT_1 and AT_2 receptor stimulation. Hayashi *et al.*[8] proposed a signaling pathway in which Ang1–7-mediated signaling serves as an antagonist of AT_1 receptor-mediated regulation of ERK1/2 activity. In their study, the ARB olmesartan almost completely inhibited the changes caused by Ang II. However, the ACE2

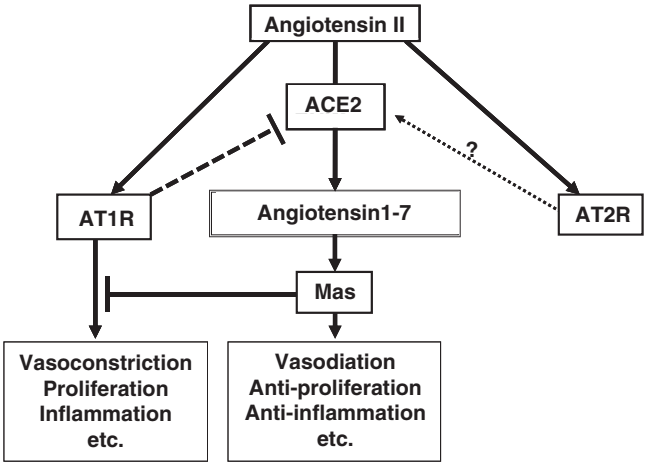

Figure 1 Possible interactions between the ACE2/angiotensin1–7/Mas axis and angiotensin II receptors. ACE, angiotensin-converting enzyme; AT_1R and AT_2R, angiotensin II receptors.

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inhibitor DX600 only partly reversed the effect of olmesartan. Similar changes were obtained with a Mas antagonist instead of DX600. These findings suggest that the separate actions of olmesartan may include inhibition of AT_1 receptor-mediated signaling and stimulation of the Ang1–7-mediated portion of the pathway.

However, it is also possible that blockage of AT_1 receptor-mediated signaling directly modulates the Ang1–7-mediated pathway (Figure 1). A previous report indicated that treatment with an ARB increased the activity and expression of ACE2 in cardiomyocytes treated with Ang II.[7] These results suggest that AT_1 receptor stimulation decreased the Ang1–7-mediated pathway by reducing the Ang1–7 level associated with ACE2 activity. In addition, it is also possible that an ARB directly increases ACE2 activity and Ang1–7 production. It is difficult to distinguish the direct action of an ARB from its effects on AT_1 receptor blockage. However, if there are some different characteristic effects on ACE2/Ang1–7 activation among ARBs, it may suggest their direct and specific actions.

Previous reports indicate that AT_2 receptor stimulation is involved in the inhibitory actions of ARB.[13] As the vascular actions of Ang1–7 are similar to those of AT_2 receptor stimulation, it is possible that AT_2 receptor stimulation also modulates the production of Ang1–7. The interaction between AT_2 receptor-mediated signaling and the ACE2/Ang1–7/Mas axis has not yet been well clarified.

Although the detailed mechanism of interaction of Ang1–7/Mas with AT_1 or AT_2 receptor stimulation should be further investigated, the ACE2/Ang1–7/Mas axis may become an important target of renin–angiotensin system for a therapeutic approach to cardiovascular diseases.

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