Regulation of ACE2 and ANG-(1–7) in the aorta: new insights into the renin-angiotensin system in the control of vascular function

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THE RENIN-ANGIOTENSIN SYSTEM (RAS) plays a key role in the control of cardiovascular function. Normal activity of the RAS has been physiologically implicated in maintaining homeostasis of arterial pressure and hydroelectrolyte balance as well as in modulating cell growth and differentiation. In contrast, abnormal activation of the RAS has been associated with the pathophysiology of cardiovascular diseases such as hypertension, myocardial infarction, and heart failure (7, 17). For decades, the octapeptide angiotensin II (ANG II), formed from the degradation of the angiotensin decapptide (ANG I) by angiotensin-conversion enzyme (ACE), has been considered the major bioactive compound of the RAS. The interaction of ANG II with its type 1 receptor (AT1R) results in a wide spectrum of effects including sodium and water retention, vasoconstriction, and myocyte and vascular smooth muscle cell growth (23, 24). As a counterbalance, ANG II also interacts with the type 2 receptor (AT2R), inducing effects that oppose many of the AT1R-mediated actions of ANG II (2).

During the last decade, it has become clear that other ANG peptides formed within the RAS cascade also make significant contributions to the broad spectrum of RAS actions (12). Of special interest is the heptapeptide ANG-(1–7), which has gained attention among scientists because of cumulative evidence showing that ANG-(1–7) antagonizes many of the cardiovascular actions of ANG II (6, 21). ANG-(1–7) can be generated from both ANG I and ANG II by the action of the recently described ACE-related enzyme ACE2. Levels of ANG-(1–7) increase significantly during ACE inhibition because of an increase in the ANG-(1–7) precursor (ANG I) and also because ACE is one of the main metabolizing enzymes of ANG-(1–7) (19). Accumulating evidence indicates that ANG-(1–7) exerts direct pharmacological and physiological actions in the cardiovascular system that include vasodilation, improvement of cardiac function, and inhibition of cell proliferation (7, 8). Furthermore, it has been suggested that the accumulation of ANG-(1–7) during treatment with ACE inhibitors is as important as the observed decrease in ANG II generation in the protection of the cardiovascular system afforded by ACE inhibition (3, 22).

Along with the increasing interest in the cardiovascular effects of ANG-(1–7), the actions of the ACE2 enzyme, which catalyzes ANG-(1–7) generation, have met with growing attention. ACE2 is the first known homolog of ACE and was cloned only 5 years ago from a human heart cDNA library generated from heart failure patients (5). It has been hypothesized that ACE2 protects against the progression of cardiovascular disease, whereas ACE2 deficiency promotes cardiovascular disease. Studies in ACE2 knockout mice have demonstrated that the lack of this enzyme is associated with impaired cardiac contractility and consequent abnormal heart function (4). Moreover, associations between ACE2 and hypertension have also been reported. In the spontaneously hypertensive rat (SHR), the levels of renal ACE2 mRNA and protein expression were markedly less than in the normotensive Wistar-Kyoto rat (1).

In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, Igase et al. (11) provide new information regarding the actions of ACE2 that has therapeutic implications for the treatment of hypertension and the associated complications. This study shows, for the first time, the presence of ACE2 in the thoracic aorta of the SHR and furthermore demonstrates that sustained blockade of the AT1R leads to upregulation of ACE2 expression in this tissue. Chronic treatment with the AT1R antagonist olmesartan induced a fivefold increase in ACE2 mRNA in the SHR aorta, which led to a significant increase in aortic ANG-(1–7) protein expression. These effects were associated with significant decreases in aortic medial thickness and, therefore, may represent an important protective mechanism in the prevention of cardiovascular events in hypertensive subjects.

Previously, studies on the hemodynamics of hypertension had focused primarily on the regulation of cardiac output, fluid volume, and vascular resistance (9). Recently, investigators have concentrated on the contribution of large artery disease in the progression of hypertension and associated cardiovascular complications (13, 15, 18). In general, hypertensive aortas are hypertrophied, and the external tension is higher than the internal tension compared with normotensive arteries, which hampers the ability of flow to modulate arterial diameter (13, 18). The decreased compliance of the aorta due to an augmented wall thickness and abnormal stiffness is responsible for left ventricular overload and the subsequent left ventricular hypertrophy (10, 14). The increasing data showing an association between aortic compliance and cardiovascular risk have raised interest in finding interventions that specifically reduce vascular remodeling. Recent studies have shown that by opposing the vasoconstrictor and hypertrophic effects of ANG II on the vessel wall, treatment with ACE inhibitors are effective in reducing arterial remodeling (16, 20). ACE inhibitors also promote ANG II antiproliferative actions by increasing the generation of ANG-(1–7) in the vasculature (22).

In this issue, Igase et al. (11) demonstrate that AT1R antagonists effectively prevent aortic hypertrophy not only by blocking the actions of ANG II but also by increasing aortic ACE2 and ANG-(1–7) expression. These findings may lead to new applications for AT1R antagonists in the prevention of cardiovascular disease, especially because AT1R antagonists have...
been shown to possess beneficial effects on ANG-(1–7) expression and vascular remodeling that are similar to ACE inhibitors while lacking some of the adverse effects associated with ACE inhibition (e.g., dry cough). This study also addresses an open question in the RAS field, i.e., does high blood pressure affect ACE2 expression? Because atenolol and hydralazine treatment decreased blood pressure but did not affect vascular ACE2 expression, this study has established that the expression of ACE2 is not necessarily associated with changes in blood pressure (as has been proposed) but rather is associated with a direct action of the RAS on ACE2.

From the data presented, it is not possible to determine the mechanism underlying the effects of AT1R antagonism on the expression of aortic ACE2 and ANG-(1–7). Does interaction of ANG II with the AT1R trigger a signal transduction pathway that results in the inhibition of ACE2 expression that is blocked by AT1R antagonism or does AT1R blockade increase ACE2 expression by ANG II activation of AT2R signaling events? Among other studies, it would be interesting to determine whether selective AT2R agents affect ACE2 and ANG-(1–7) expression and whether these effects modulate vascular remodeling.

In summary, this study by Igase et al. (11) reveals further complexities of the RAS in a model of cardiovascular disease by demonstrating that AT1R antagonism increases aortic ACE2 and ANG-(1–7) in the SHR concomitantly with inhibition of vascular remodeling. In so doing, new light is shed on our understanding of the role of the RAS in the regulation of vascular function. Determining the exact mechanisms involved in this newly revealed action of an AT1R antagonist on ACE2 expression could lead to the development of new therapeutics for selectively stimulating ACE2 and ANG-(1–7) expression, which may have significant impact in the treatment of cardiovascular disease.

REFERENCES