Local Renin Angiotensin Aldosterone Systems and Cardiovascular Diseases

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KEYWORDS

• Local renin angiotensin • Expression • Internalization • Cardiovascular diseases

KEY POINTS

- The presence of local renin angiotensin aldosterone systems (RAAS) in the cardiovascular and renal tissues and their influence in cardiovascular and renal diseases are described.
- The fundamental role of ACE/Ang II/AT1 receptor axis activation as well the counter regulatory role of ACE2/Ang (1–7)/Mas receptor activation on cardiovascular and renal physiology and pathology are emphasized.
- Special emphasis is given to the influence of the intracrine components of the RAAS, including Ang II and renin, on the regulation of cell communication, the incidence of cardiac arrhythmias, and remodeling.
- Recent findings showing the role of intracellular Ang II on membrane potential and tone of vascular resistance vessels, in opposite to that seen with extracellular Ang II and their implications for vascular remodeling and hypertension are described.
- The presence of a local renin angiotensin system and its influence on hypertension is discussed and, finally, the hypothesis that epigenetic factors change the RAAS in utero and induce the expression of renin or Ang II inside the cells of the cardiovascular system is presented.

ON THE ROLE OF CONVENTIONAL RENIN ANGIOTENSIN ALDOSTERONE SYSTEMS

The activation of the conventional renin angiotensin aldosterone system (RAAS) plays a seminal role on the physiologic regulation of blood volume and blood pressure and it is involved on the regulation of cardiac and renal functions. Renin released from the kidney converts angiotensinogen from the liver to the decapeptide angiotensin-I, which undergoes proteolytic cleavage generating angiotensin-II (Ang II) through the activation of angiotensin-converting enzyme (ACE) (**Fig 1**). During hypertension, heart failure, and myocardial ischemia, the permanent activation of RAAS is involved in cardiac and vascular remodeling, including left ventricular hypertrophy and fibrosis.

The beneficial effects of ACE inhibitors and Ang II–type 1 receptor blockers (ARBs) in hypertensive patients and the improvement of cardiac function and remodeling in

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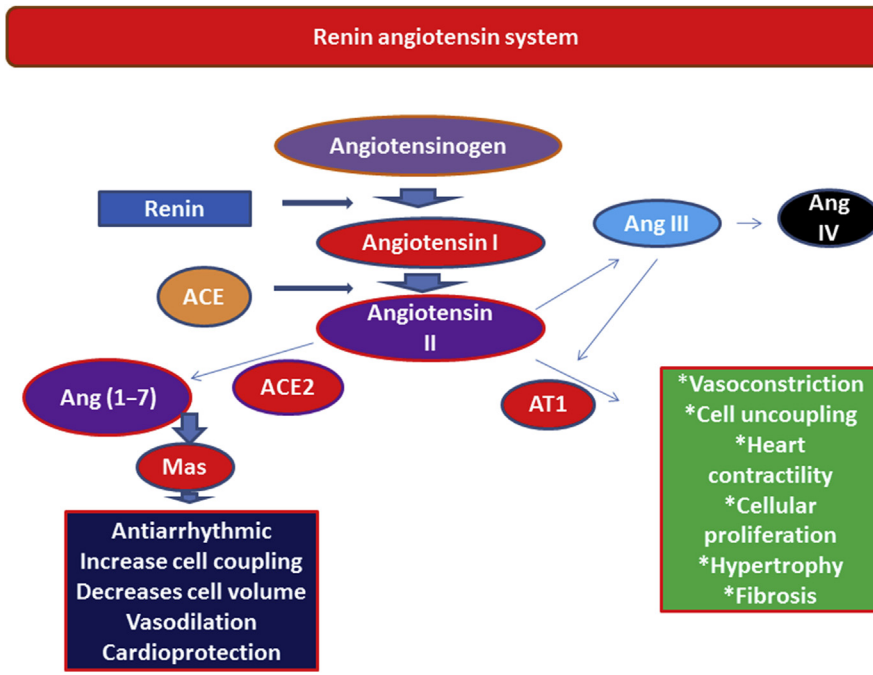

Fig. 1. The conventional RAAS including the opposite effects of Ang II and Ang (1–7) on cardiovascular pathophysiology. Furthermore, the new peptides angiotensin III (Ang III) and angiotensin IV (Ang IV) with its respective receptor (AT4) were represented.

patients with heart failure, is an indisputable evidence of the harmful effect of Ang II.[1–5] Large clinical trials like the Survival and Ventricular Enlargement (SAVE) Trial and the Veterans Administration Cooperative Study Treatment Group revealed the beneficial role of ACE inhibitors in patients with myocardial infarction as well as during hypertension.[1–8] Ang II type 1 receptor blockers also reduce the incidence of interstitial fibrosis by decreasing collagen I gene expression, which is an important factor in the etiology of left ventricular hypertrophy and diastolic dysfunction.[9]

Recent developments indicate that the classic ACE/Ang II/AT1 receptor axis is not the only signal pathway involved in the activation of RAAS, but other pathways like the ACE2/Ang (1–7)/Mas receptor axis play a fundamental role counteracting many effects of Ang II in the cardiovascular and renal systems. ACE2, an enzyme having a high homology to ACE, is able to hydrolyze Ang II to the peptide angiotensin (1–7) (Ang [1–7]),[10,11] which counteracts many effects of Ang II, including its pressor effect as well as to the proliferative and profibrotic effects of peptide.[12–17] Ang (1–7) also reduces the incidence of heart failure after myocardial infarct in rats, and in humans it increases the coronary perfusion and aortic endothelial function[18] with beneficial effect for patients with coronary insufficiency and hypertension. The electrical remodeling is also reduced by Ang (1–7) with consequent increase of the conduction velocity in the failing heart, thereby reducing the incidence of cardiac arrhythmias.[15,16]

More recently, it was found that the activation of the ACE2-Ang (1–7)-Mas receptor axis is involved in the regulation of heart cell volume.[19] The heptapeptide, for instance, decreases the cell volume and the swelling-activated chloride current (ICl_{swell}), an effect inhibited by ouabain what supports the view that Ang (1–7) activates the sodium