Editorial Comment

ARBs or ACEIs, That Is the Question

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The renin-angiotensin system (RAS) plays a pivotal role in the maintenance of body fluid, electrolyte homeostasis and cardiovascular functions. It is widely accepted that its impairments in cardiovascular tissue both locally and systemically cause progressive cardiovascular remodeling, and ultimately result in morbidity and mortality for human beings. Therefore, disruptions to this system by angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are currently utilized as one of the major medical treatment options available among physicians. However, emerging evidences indicate that angiotensin (1-7) (Ang-(1-7)) is an endogenous counteracting peptide against RAS and its end product, angiotensin II (Ang II). Ang-(1-7) and its synthesis in the body have become a focus of much interest (*1*, *2*). There are three *in vivo* pathways that can potentially generate Ang-(1-7), as shown in Fig. 1 (*3*, *4*). Among these pathways, angiotensin converting enzyme 2 (ACE2), which was discovered as an ACE homologous carboxymonopeptidase by Donoghue *et al*. (*5*, *6*), and which includes an N-terminal signal sequence, a single active-site catalytic region, and a C-terminal hydrophobic membrane-anchor region, is thought to be the most important enzymatic mediator for the catabolic cleavage from an octa-peptide, Ang II, to a hepta-peptide, Ang-(1-7). Discovery and establishment of this new bioactive endocrine system provoked various new insights not only into cardiovascular medicine but also into pharmacological dissections of ARBs and ACEIs. In an article appearing in this issue of *Hypertension Research* (*7*), Agata *et al*. provide new evidence that olmesartan, one of the most potent ARBs, exerts a pharmacological action to lower blood pressure by modifying the Ang-(1-7)/ACE2 system. They examined the Ang-(1-7)/ACE2 system during chronic olmesartan treatment of stroke-prone spontaneously hypertensive rat (SHR-SP), a rodent model of hypertension. They found that olmesartan treatment increased ACE2 expression in the kidney and heart, and enhanced the action of Ang-(1-7), using Ang-(1-7) antagonist with restoring Ang II elevation *in vivo*. They speculated that ACE inhibition by elevated Ang-(1-7) leads to Ang II suppression, which is recognized as a unique feature of olmesartan treatment (*8*). Whether these multiphasic pharmacological potentials only apply to olmesartan are still unclear. However, it has already been shown that the endogenous enhancement of Ang-(1-7) *in vivo*—both through elevated production and degraded inhibition—makes a nonnegligible contribution to the pharmacological actions of ACEI treatment (Fig. 1) (*9*, *10*). In their recent review analysis of multiple clinical trials, Verma and Strauss raise the question "Are ARBs equal to ACEIs without cough?" (*11*). Independent of their conclusions about ACEIs and ARBs, the difference between these drug classes should be reviewed in detail from the standpoint of the Ang-(1-7)/ACE2 system. Thus, complicated interactions between newly discovered and more established pathways of the RAS will need to be brought to light, and, in the future, multilayered pharmacological interventions could be developed to provide more optimized treatment options for hypertensive cardiovascular diseases.

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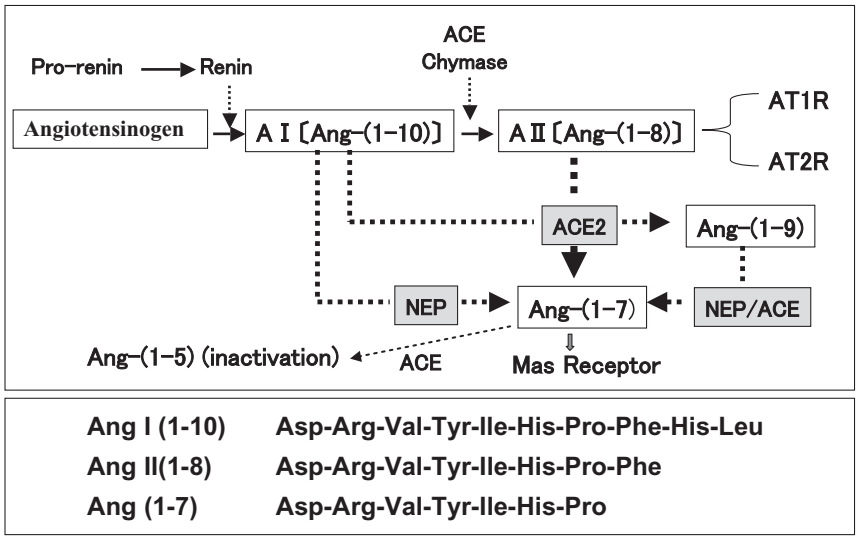

Fig. 1. *Current metabolic map for RAS and Ang-(1-7)/ACE2 system and the structures of angiotensin peptides. Modified from: Ferrario* et al*. (*12*). NEP, neutral endopeptidase.*

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