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COMMENT

Novel aspects of the renin-angiotensin system for pulmonary arterial hypertension

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Keyword Pulmonary hypertension · Renin–angiotensin system · Alamandine · Masrelated G protein coupled receptor

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Pulmonary arterial hypertension (PAH) affects approximately 1% of the global population and 10% of individuals over 65 years of age. The first case of PAH was reported by Dr. Ernst von Romberg reported first case who, at autopsy, showed thickening of the pulmonary artery without underlying heart and lung disease [1]. Then, Dr. David Dresdale in the United States reported several cases with a definition of pulmonary primary hypertension [2], which is a term no longer used. The term "primary pulmonary hypertension" was first used at a World Health Organization meeting in Geneva in 1973 [3]. At the time, this condition was regarded as an orphan disease, and the majority of patients who received this diagnosis would die as a result because there were no effective medical treatments available. In 1982, Bruck A. Reitz reported that heart-lung transplantation is effective [4]. Later, the remodeling and recovery capabilities of the right ventricle were discovered and patients were treated only with lung transplantation [5].

In the last 3 decades, intensive studies on the pathogenesis of endothelial dysfunction and pulmonary vascular remodeling, which play major roles in the pathophysiology of PAH, have shown that endothelin, nitric oxide, and prostacyclin pathways have been identified as important therapeutic targets for PAH. As a result, various targeted PAH treatments were developed and are currently being used either alone or in combination. The anatomopathological classification in current guidelines is an important development in improving the diagnosis, follow-up, and treatment strategies of PAH. The fact that many treatments that looked promising during preclinical studies have minimal effectiveness during subsequent clinical testing—a translational gap commonly referred to as the Valley of Death [6]—indirectly emphasizes the limitations of PAH animal studies.

In this issue of *Hypertension Research*, Shen and colleagues [7] did tremendous work by examining the protective effect of losartan in an ethanol-induced PAH model and showed that ethanol injection elevated pulmonary arterial pressure in swine. The concentration of renin-angiotensin system (RAS) ligands elevated in plasma but not in the pulmonary artery. The level of oxidative stress increased in both plasma and pulmonary artery. In conclusion, the authors stated that losartan partially inhibited the acute elevation of pulmonary arterial pressure after all sessions of ethanol injection, and moderately reversed the ethanol-induced pulmonary artery remodeling by inhibiting oxidative stress and P38 MAPK signaling. The experimental study is unique and has seminal observations.

Renin-angiotensin system was discovered with renin, a pressor chemical by Tigerstedt and Bergmann in 1898 [8]. Since this discovery, our understanding of the RAS system has continued to advance in the pathophysiology and treatment of cardiovascular diseases. First, the decapeptide Ang I from the amino terminus of angiotensinogen is cleaved by the enzyme renin, which is released into the bloodstream from the juxtaglomerular cells in such cases as hypotension, increased sympathetic tone, specialized smooth muscle cells in glomerular arterioles in the kidneys. Then, Leonard T. Skeggs' discovered the angiotensin-converting enzyme of which removed the carboxy-terminal dipeptide of Ang I to produce the octapeptide Ang II [9]. Ang II, through the angiotensin II type 1 receptor—a G protein-coupled receptor—causes vasoconstriction, and sodium retention, which leads to the retention of water, and aldosterone secretion, cardiac and vascular activation promotes endothelial dysfunction and cardiac remodeling [10]. The investigated agent in this study, losartan acts by blocking this classical pathway at the receptor level.

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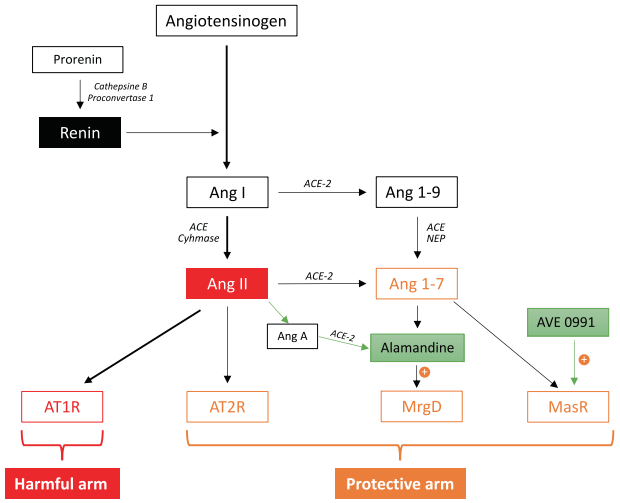


Fig. 1 Classical pathway and novel components of the RAAS. The heavy arrows show the classical pathway, and the light arrows indicate alternative pathways and novel components. ACE Angiotensin converting enzyme, Ang Angiotensin, AT1R Angiotensin II type I receptor, AT2R Angiotensin II type I receptor, MrgD Mas-related G protein-coupled receptor D, MasR Mitochondrial assembly receptor

In the alternative RAS pathway, ACE 2/Ang (1–7)/MasR and ACE-2/Ang (1–7)/MrgD pathways have been defined, which opposes the vasoconstrictor and pathological effects of the ACE/Ang II/AT1R axis [11]. ACE2, a homologue of ACE, is responsible for producing Ang (1–7) by cleaving Ang II. Ang (1–7) binds and activates G protein-coupled Mas (mitochondrial assembly-1) receptor to exert antiinflammatory, antihypertensive, and antiremodeling effects [12]. While AVE0991 is a non-peptide and orally active compound that has protective effects on the vessels, kidneys, and heart by binding to the Mas receptor, Alamandine is formed as a result of decarboxylation of the Asp1 residue from Ang (1–7) to the Ala1 residue at the N-terminus. Alamandine exerts its vasodilatory and antifibrotic effects similar to Ang (1–7) through MrgD (Mas-related G protein coupled receptor D) [13]. In the present study, the authors have detected that the gene expression level of AT2R did not change significantly throughout the whole experiment. However, the nitric oxide level of pulmonary artery tissue was downregulated significantly after ethanol injections and could not be reversed by losartan. These might be the clues for the impairment of Mas and MrgD receptors in acute elevation of pulmonary arterial pressure. However, whether the vasodilatory Mas/MrgD receptors played a protective role in the acute elevation of pulmonary arterial pressure needs further well-designed experimental studies (Fig. 1). Indeed, this will be a good starting point with exciting prospects.

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Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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