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EDITORIAL

The renin-angiotensin-aldosterone system: a new look at an old system

Shin-ichiro Miura[1,2]

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It is a great honor and pleasure for me to serve as an Associate Editor of Hypertension Research in 2023. This is an exciting time for my research. Our group has been studying angiotensin II (Ang II) type 1 (AT1) and type 2 receptor-induced structure and function and the efficacy of their blockers [1–5]. Ang II is an active octapeptide hormone in the renin-angiotensin aldosterone system (RAAS). Research on the RAAS began with the discovery of renin by Prof. Tigerstedt in 1898, more than 120 years ago [6]. In Japan, Prof. Arakawa isolated human Ang II for the first time and determined its structure in 1967 [7]. Since then, RAAS has been shown to play a critical role in elevating blood pressure (BP) and is now a target of antihypertensive medications; many types of drugs such as angiotensin converting enzyme inhibitors (ACE-Is), AT1 receptor blockers (ARBs), aldosterone blockers and renin inhibitors have been developed and are now used clinically worldwide. RAAS inhibitors have not only antihypertensive effects, but also cerebro-cardio-renal protective effects independent of their antihypertensive effects.

In research on RAAS, many new discoveries and antihypertensive drugs have been inspired based on previous research by many predecessors. A PubMed search for RAAS yields more than 6,000 hits in 2022 alone, and it is still an important topic in the fields of hypertension and cardiovascular research. Regarding the RAAS, many new findings were published in Hypertension Research in 2022 (Table 1). Here, we introduce several selected important reports on RAAS research. In a basic science study, Zuo et al. investigated the regulatory mechanisms of the novel circ_0018553 in Ang II-induced cardiac hypertrophy [8]. Endothelial progenitor cell-derived exosomal circ_0018553 protected against Ang II-induced cardiac hypertrophy by modulating the miR-4731/ sirtuin 2 signaling pathway. Next, Shokoples et al. hypothesized that Ang II-induced BP elevation and vascular injury may be blunted in interleukin 23 receptor (IL23R) knock-in mice that are deficient in functional IL23R [9]. The authors concluded that functional IL23R deficiency was associated with increased interferon-γ-producing T cells and exaggerated initial development of Ang II-induced hypertension, and was in part mediated by interferon-γ. Thus, crosstalk with various intracellular signals having unclear relationships with Ang II-mediated signals is still reported.

✉ Shin-ichiro Miura
miuras@cis.fukuoka-u.ac.jp

[1] Department of Cardiology, Fukuoka University School of Medicine, Fukuoka 814-0180, Japan

[2] Department of Internal Medicine, Fukuoka University Nishijin Hospital, Fukuoka 814-8522, Japan

Table 1 The renin-angiotensin-aldosterone system: a new look at an old system published in Hypertension Research in 2022

Basic research
✓ Protection against Ang II-induced cardiac hypertrophy by circ_0018553 [8]
✓ Exaggerated development of Ang II-induced hypertension by IL-23R deficiency [9]
Clinical research
✓ Efficacy of MR antagonists in the treatment of DKD [10]
✓ Efficacy and safety of sacubitril/valsartan in patients with essential hypertension [11]
✓ Safety of a selective inhibitor of aldosterone synthase, Baxdrostat [12]

Ang II angiotensin II, *IL23R* interleukin 23 receptor, *MR* mineralocorticoid receptor, *DKD* diabetic kidney disease

New findings have been also published the field of clinical research. First, ACE-Is and ARBs are useful for the treatment of diabetic kidney disease (DKD), and the use of an ACE-I or ARB alone does not provide sufficient efficacy. Sato et al. summarized the latest evidence regarding the use of non-steroidal mineralocorticoid receptor (MR) antagonists in the treatment of DKD [10]. In DKD treatment, they indicated that it is important to continue to use MR antagonists without interruption through the combined use of a new oral potassium adsorbent against hyperkalemia. Second, Rakugi et al. evaluated the efficacy and safety of sacubitril/valsartan compared to those of olmesartan in Japanese patients with mild to moderate essential hypertension [11]. Sacubitril/valsartan was the first approved treatment for heart failure (HF) in the world. HF can be divided into HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). The prognosis of HFpEF is as equally poor as that of HFrEF. However, at present, there is no medication approved as a direct therapeutic target for HFpEF. Although the etiology of HFpEF is multifactorial, most patients are associated with hypertension. Therefore, first, if sacubitril/valsartan can be administered as an antihypertensive medication, it may be possible to suppress the transition to HFpEF. Treatment with sacubitril/valsartan was shown to be effective and provided superior BP reduction; among patients with essential hypertension, a higher proportion achieved target BP levels than those who were treated with olmesartan. Finally, although a selective inhibitor of aldosterone synthase has long been studied as an inhibitor of aldosterone, a new report on the safety of Baxdrostat has been published [12].

In conclusion, the onset and progression of hypertension and cardiovascular diseases due to RAAS is still a central research theme, although this system has been studied for more than 120 years. Many new findings are expected to be published in the future.

Compliance with ethical standards

Conflict of interest SM has received honoraria from Otsuka Pharma Co. Ltd., Daiichi-Sankyo Co. Ltd., Novartis, Bayer Yakuhin Ltd., and Boehringer Ingelheim. SM has received grants from Otsuka Pharma Co. Ltd., Astellas Pharma Inc., Daiichi-Sankyo Co. Ltd., Novartis, Bayer Yakuhin Ltd., MSD Co. Ltd. and Boehringer Ingelheim.

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