J Pharmacol Sci **113**, 289 – 291 (2010)

Journal of Pharmacological Sciences

Forum Minireview

New Approaches to Blockade of the Renin–Angiotensin–Aldosterone System: Overview of Regulation of the Renin–Angiotensin–Aldosterone System

Akira Nishiyama[1,*] and Shokei Kim-Mitsuyama[2]

[1]*Department of Pharmacology, Faculty of Medicine, Kagawa University, Kagawa 761-0793, Japan*
[2]*Department of Pharmacology and Molecular Therapeutics, Kumamoto University Graduate School of Medical Sciences, Kumamoto 860-8556, Japan*

Received March 26, 2010; Accepted June 3, 2010

Abstract. The critical role played by the renin–angiotensin–aldosterone system (RAAS) in the regulation of blood pressure and body fluid homeostasis has been well recognized. Angiotensin (Ang) II and aldosterone are the most powerful biologically active products of the RAAS, although there are also other bioactive Ang peptides involved in this system, including AngIII, AngIV, and Ang1 – 7. In addition to their physiological roles, AngII and aldosterone induce inflammation, cell growth, mitogenesis, apoptosis, migration, and differentiation; regulate gene expression of bioactive substances; and activate multiple intracellular signaling pathways, all of which contribute to cardiovascular tissue injury. During the last decade, both clinical and preclinical studies have demonstrated that various pharmacological interventions of the RAAS exert blood pressure–independent cardiovascular-protective effects. In this Forum Minireview entitled "New approaches to blockade of the renin–angiotensin–aldosterone system", we will discuss the impact of RAAS inhibitors on prevention of the development of hypertension and cardiovascular diseases. Before going into details about the insights into RAAS inhibition that each of the four groups will provide, we herein briefly overview our current understanding of regulation of the circulating RAAS.

Keywords: angiotensin II (AngII), aldosterone, AngII type 1 (AT_1) receptor, mineralocorticoid receptor (MR)

1. Introduction

In recent years, the attention that had been paid upon the renin–angiotensin–aldosterone system (RAAS) as a hypertension promoter has shifted to the role it plays in the progression of cardiovascular injury. Large-scale clinical trials on the pharmacological effects of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin (Ang) II type 1 (AT_1)-receptor blockers (ARBs) support the notion that AngII and aldosterone exert a cardinal role in the pathogenesis of cardiovascular diseases (1, 2). Accordingly, most national guideline groups now recommend the use of ACEIs or ARBs in preference to other antihypertensive agents for hypertensive patients with cardiovascular disease (3 – 6). Furthermore, beneficial effects of mineralocorticoid receptor (MR) blockers on cardiovascular diseases, independent of the effects exerted by the renin–angiotensin system (RAS) inhibitors, have been reported in several studies. The Randomized Aldactone Evaluation Study (RALES) (7) and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficiency and Survival Study (EPHESUS) (8) demonstrated that adding MR blockers to standard therapies, including ACEIs or ARBs, significantly reduced morbidity and mortality in patients with heart failure. Based on the results from these two multicenter clinical trials and other studies, MR blockers, in addition to RAS inhibitors, are recommended for the treatment of hypertension in patients with cardiovascular diseases (2).

In this Forum Minireview entitled "New approaches to

*Corresponding author. akira@kms.ac.jp
Published online in J-STAGE on July 27, 2010 (in advance)
doi: 10.1254/jphs.10R03FM

blockade of the renin–angiotensin–aldosterone system", which is based on the symposium at the 82nd Annual Meeting of The Japanese Pharmacological Society held on March 2009 in Yokohama, Japan, we will discuss the effects of the RAAS inhibitors in preventing the development of hypertension and cardiovascular diseases. Before introducing the detailed investigations undertaken by our forum members, we herein briefly provide an overview of our current understanding of the regulation of the circulating RAAS.

2. Regulation of the systemic RAAS pathways

Figure 1 shows the circulating RAAS pathways and the concentrations of the RAAS components. Angiotensinogen is primarily formed and constitutively secreted by hepatic cells into the circulation (9). On release into the circulation, active plasma renin cleaves angiotensinogen to form a decapeptide, AngI (10). Circulating renin and its precursor, prorenin, are released primarily from the juxtaglomerular cells located in the glomerular afferent arterioles (11, 12). However, other tissues also secrete prorenin into the circulation, and prorenin can be converted to renin by limited proteolysis (11, 12). As shown in Fig. 1, circulating angiotensinogen is abundant; 1,000 times as much as AngI and AngII. Thus, renin activity determines the rate of AngI formation in the plasma with huge stores of circulating angiotensinogen (1). Namely, even a small relative change in plasma renin activity may make a large absolute difference in circulating AngI and AngII levels.

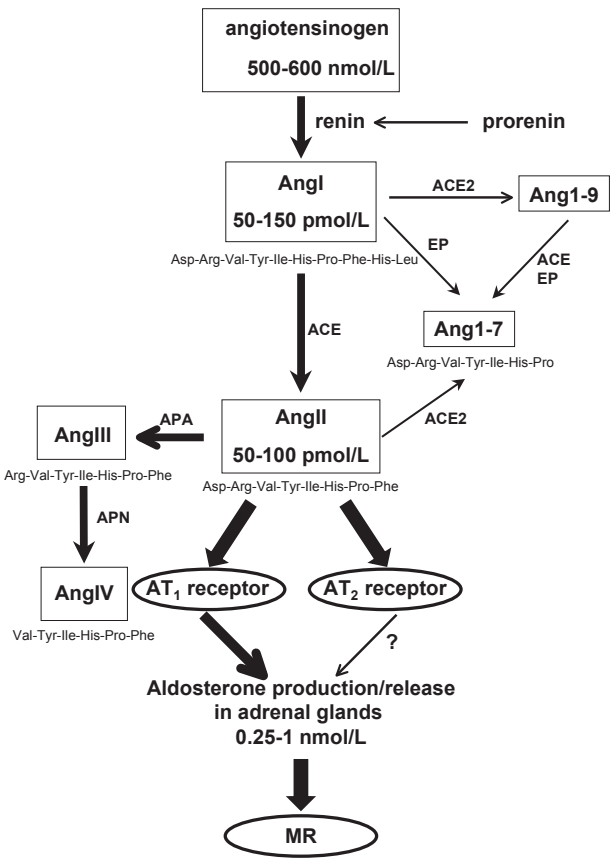

Fig. 1. Brief scheme of the systemic RAAS. The representative plasma concentrations for angiotensinogen, AngI, AngII, and aldosterone in anesthetized rats are shown. EP, endopeptidase; APA, aminopeptidase A; APN, aminopeptidase N.

Circulating AngI is easily converted to AngII, due not only to the circulating ACE (dipeptidyl carboxypeptidase) but also to the widespread presence of ACE on endothelial cells of many vascular beds including the lung (11). Although other pathways for AngII formation have been identified in certain tissues, the circulating levels of AngII primarily reflect the consequences of the enzymatic cascade of renin and ACE that catalyzes the breakdown of angiotensinogen into the end-product of the RAAS, AngII (11). Several angiotensinases and peptidases are then able to metabolize AngII further (12). Although AngIII, AngIV, and Ang1 – 7 also have biological activity, their plasma levels are much lower than that of AngII (1). In many organs and tissues, their local formation is of major significance in the regulation of Ang peptide levels, which has been well reviewed by Kobori et al. (1) and will not be discussed here.

The AngII receptor belongs to the class of seven-transmembrane G-protein–coupled receptors (13). Two major categories of AngII receptors, type 1 (subtypes 1a and 1b in rodents) and type 2, have been cloned (13). However, most of the AngII hypertensinogenic actions are generally attributed to the AT_1 receptors (1). The AT_1 receptor is widely expressed in various cardiovascular and renal tissues (1, 13). On the other hand, the AT_2 receptor is highly expressed in organ mesenchyme during fetal life and decreases dramatically after birth (14). Although the role of the AT_2 receptor still remains uncertain, it has been suggested that AT_2-receptor activation counteracts AT_1-receptor effects (14). Many studies have indicated that in adrenal glands, AngII stimulates aldosterone production and secretion through the activation of AT_1 receptors (15). However, as shown in Fig. 1, it has also been suggested that AT_2 receptor is involved in adrenal aldosterone production during the long treatment with ARBs and ACEIs (16). Aldosterone plays a powerful role in sodium reabsorption and potassium excretion through the activation of MR in tubular epithelial cells. In addition to its vital role in electrode homeostasis, accumulating evidence also suggests that aldosterone is a key factor in mediating cardiovascular injury (17).

3. Conclusions

Before going into the details of RAAS inhibition, which will be presented by each of the four groups (18 – 21), we herein briefly overviewed how the circulating RAAS is regulated. Based on the preclinical and clinical evidence, it is now clear that the RAAS plays an essential role in the development of hypertension and cardiovascular diseases.

References

1 Kobori H, Nangaku M, Navar LG, Nishiyama A. The intrarenal renin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. Pharmacol Rev. 2007;59: 251–287.

2 Nishiyama A, Hitomi H, Rahman A, Kiyomoto H. Drug discovery for overcoming chronic kidney disease (CKD): pharmacological effects of mineralocorticoid-receptor blockers. J Pharmacol Sci. 2009;109:1–6.

3 Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation. 2007;115:114–126.

4 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2007;25:1105–1187.

5 The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, et al. Hypertens Res. 2009;32:3–107.

6 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289: 2560–2572.

7 Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341:709–717.

8 Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348:1309–1321.

9 Kobori H, Ozawa Y, Suzaki Y, Prieto-Carrasquero MC, Nishiyama A, Shoji T, et al. Young scholars award lecture: Intratubular angiotensinogen in hypertension and kidney diseases. Am J Hypertens. 2006;19:541–550.

10 Navar LG, Nishiyama A. Why are angiotensin concentrations so high in the kidney? Curr Opin Nephrol Hypertens. 2004;13: 107–115.

11 Ichihara A, Kobori H, Nishiyama A, Navar LG. Renal renin-angiotensin system. Contrib Nephrol. 2004;143:117–130.

12 Navar LG, Nishiyama A. Intrarenal formation of angiotensin II. Contrib Nephrol. 2001;135:1–15.

13 Kim S, Iwao H. Molecular and cellular mechanisms of angiotensin II-mediated cardiovascular and renal diseases. Pharmacol Rev. 2000;52:11–34.

14 Navar LG, Inscho EW, Majid SA, Imig JD, Harrison-Bernard LM, Mitchell KD. Paracrine regulation of the renal microcirculation. Physiol Rev. 1996;76:425–536.

15 Mulrow PJ. Angiotensin II and aldosterone regulation. Regul Pept. 1999;80:27–32.

16 Naruse M, Tanabe A, Sato A, Takagi S, Tsuchiya K, Imaki T, et al. Aldosterone breakthrough during angiotensin II receptor antagonist therapy in stroke-prone spontaneously hypertensive rats. Hypertension. 2002;40:28–33.

17 Kiyomoto H, Rafiq K, Mostofa M, Nishiyama A. Possible underlying mechanisms responsible for aldosterone and mineralocorticoid receptor-dependent renal injury. J Pharmacol Sci. 2008;108: 399–405.

18 Ueda S. New approaches to blockade of the renin–angiotensin–aldosterone system: Evidence from Randomized Controlled Trials (RCTs) of angiotensin-converting enzyme inhibitors and angiotensin II–receptor blockers – questions remain unsolved. J Pharmacol Sci. 2010;113:292–295.

19 Ichihara A, Sakoda M, Kurauchi-Mito A, Narita T, Kinouchi K, Bokuda K, et al. New approaches to blockade of the renin–angiotensin–aldosterone system: Characteristics and usefulness of the direct renin inhibitor aliskiren. J Pharmacol Sci. 2010;113:296–300.

20 Takai S, Jin D, Miyazaki M. New approaches to blockade of the renin–angiotensin–aldosterone system: Chymase as an important target to prevent organ damage. J Pharmacol Sci. 2010;113:301–309.

21 Nishiyama A, Hasegawa K, Diah S, Hitomi H. New approaches to blockade of the renin–angiotensin–aldosterone system: Mineralocorticoid-receptor blockers exert antihypertensive and renoprotective effects independently of the renin–angiotensin system. J Pharmacol Sci. 2010;113:310–314.