Trends in Cardiovascular Medicine 26 (2016) 221–228

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/tcm

Angiotensin receptor blockers: Focus on cardiac and renal injury

Somasundaram Arumugam, MPharm, PhD[a], Remya Sreedhar, MPharm, PhD[a], Rajarajan A. Thandavarayan, MPharm, PhD[a,b], Vengadeshprabhu Karuppagounder, MPharm, PhD[a], Prasanna Krishnamurthy, MVSc, PhD[b], Kenji Suzuki, MD, PhD[c], Masahiko Nakamura, MD, PhD[d], and Kenichi Watanabe, MD, PhD[a,]*

[a]*Department of Clinical Pharmacology, Niigata University of Pharmacy and Applied Life Sciences, Higashijima, Akiha-Ku, Niigata, Japan*
[b]*Department of Cardiovascular Sciences, Houston Methodist Research Institute, Houston, TX*
[c]*Department of Gastroenterology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan*
[d]*Department of Cardiology, Yamanashi Prefectural Central Hospital, Kofu, Yamanashi, Japan*

ABSTRACT

Angiotensin II, an important component of renin angiotensin system, is a potent vasopressor and its actions are mostly mediated via angiotensin II type 1 receptor (AT_1R) and role of AT_2R in counterbalancing the actions of AT_1R stimulation are under extensive research. In addition to its physiological actions, angiotensin II plays important roles in the pathogenesis of atherosclerosis, hypertension, left ventricular hypertrophy, and heart failure. The effects of angiotensin II can be blocked by either suppressing its production by blocking angiotensin converting enzyme or by antagonizing its actions on AT_1R using angiotensin II receptor blockers (ARBs). Instead of the extensive use of ARBs in the treatment of various cardiovascular diseases, proper selection of a particular ARB is crucial as the clinical condition of individual patient is different and also their economic status would play an essential role in medication compliance. Thus a critical review of the proven and promising actions of ARBs against various pathological conditions will be of great importance for the clinicians as well as for the researchers.

Key words: Renin angiotensin system, Angiotensin receptor blocker, Heart failure, Diabetes mellitus, Hypertension.

Introduction

The renin angiotensin (Ang) system (RAS) consists of angiotensinogen from liver gets converted to Ang I by renin, a protease mainly produced from the juxta-glomerular cells of the kidney. Ang I converting enzyme (ACE), a dipeptidyl carboxypeptidase mainly produced by the lungs, hydrolyzes Ang I to Ang II. Many of the physiological as well as pathological roles of RAS are mediated mostly via Ang II acting on its receptors of two categories; Ang II type 1 receptor (AT_1R) and type 2 receptor (AT_2R) both belonging to a family of G-protein coupled receptors (Fig. 1). This is central to the pathogenesis of cardiovascular (CV) disease through increase in reactive oxygen species (ROS) and oxidative stress, causing vascular inflammation and remodeling, endothelial dysfunction, and atherosclerosis with subsequent complications such as myocardial infarction (MI), stroke, chronic heart failure (HF), and renal disease [1]. Contemporary RAS inhibition includes use of ACE inhibitor (ACEI) and/or AT_1R blocker (ARB), which has become a leading therapeutic strategy in slowing the progression of HF

Disclosure: The authors declare that there are no conflicts of interests regarding this manuscript.

*Corresponding author. Tel.: +81 25 025 5267.
E-mail addresses: watanabe@nupals.ac.jp, somasundaram143@gmail.com (K. Watanabe).

http://dx.doi.org/10.1016/j.tcm.2015.06.004
1050-1738/

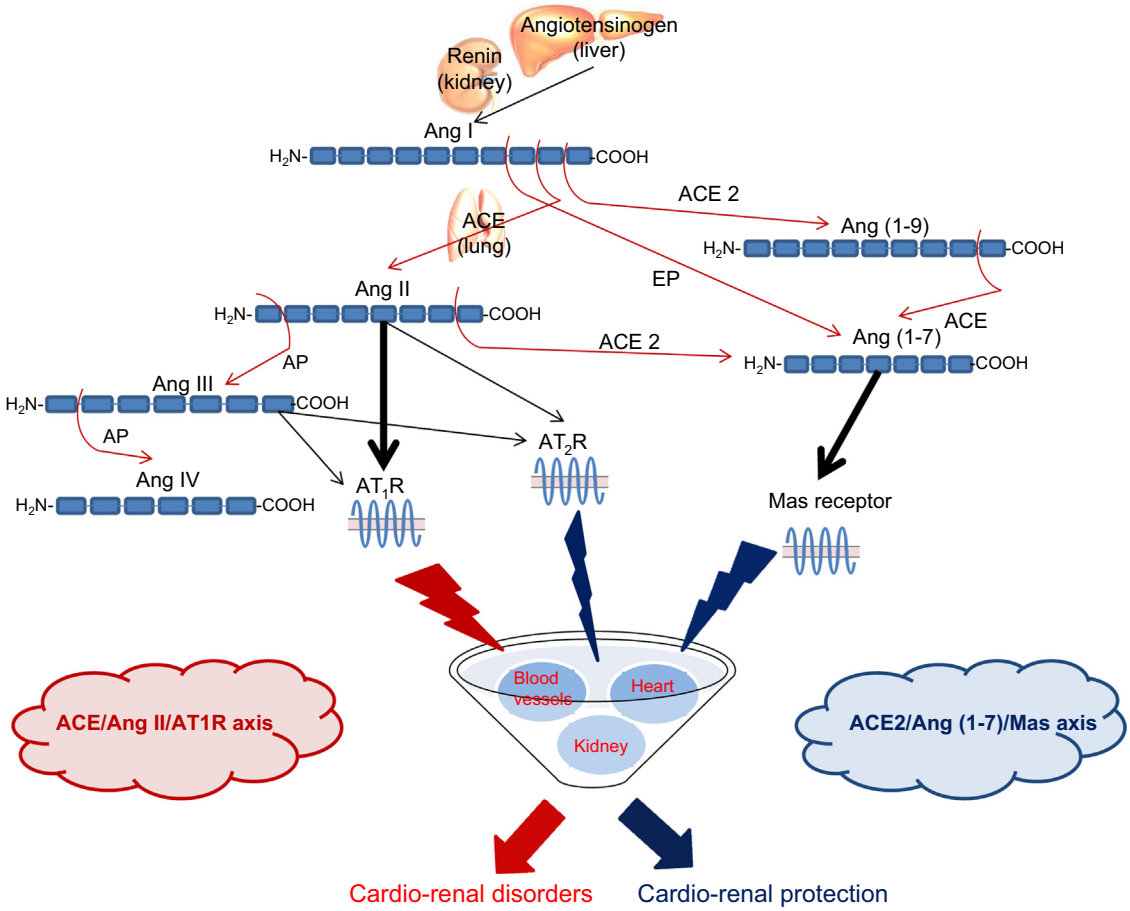

Fig. 1 – Renin angiotensin system and their components. Angiotensinogen (produced by liver) is converted to angiotensin (Ang) I by renin (produced by kidney). Ang I is converted to Ang II by Ang converting enzyme (ACE) or to Ang (1–9) by ACE2 or to Ang (1–7) by endopeptidases (EP). Ang (1–9) is converted to Ang (1–7) by ACE. Ang II is converted to Ang III and further to Ang IV by aminopeptidases (AP). Ang II and III act on Ang II type 1 receptor (AT_1R), which mediates vasoconstriction and pathological cardiac and renal remodeling. Ang II acting on AT2R causes opposite effects as that of AT1R stimulation. Ang (1–7) acts on Mas receptor causing vasodilatation and protects from adverse remodeling of heart and kidney. Left side depicts ACE/Ang II/AT1R axis and right side depicts ACE2/Ang (1–7)/Mas receptor axis. Red arrows indicate the cleavage point and thick arrows indicate the higher affinity.

and kidney diseases. ARBs have gained prominence in therapy of many pathological conditions; one possible advantage is that by blocking AT_1R, ARBs enhance Ang II activity on AT_2R. It may also influence the conversion of Ang II to other mediators of RAS such as Ang (1–7) by ACE2 that acts on Mas receptor (Fig. 1). This newer axis composed of ACE2/Ang (1–7)/Mas is suggested to produce some beneficial actions against the pathological role of Ang II. As new components and functions of RAS are being unraveled, focus is now shifting from the classical effects of RAS effectors such as regulation of intravascular volume and systemic blood pressure (BP) to their non-classical actions. Endogenous Ang II could be a key element in the immunomodulation of T-cell responses, such as activation and posterior adhesion/ transmigration activity [2]. The elucidation of such mechanisms could help to understand the Ang II-induced inflammation process and to improve treatment outcomes of immune-based diseases. We have also identified and reported the role of various ARBs against HF induced by experimental autoimmune myocarditis in rats [3,4]. Recent reports also suggest the importance of RAS blockade during diabetic complications such as cardiomyopathy, nephropathy, and neuropathy. This review focuses on the recent advances in individual ARBs (Fig. 2) as therapeutic agents against various cardiac and renal pathologies (Fig. 3). The order of the ARBs presented here is based on their popularity and not considering their efficacy or other parameters.

Telmisartan

Telmisartan is one of the widely used antihypertensive agents, which has demonstrated favorable safety and tolerability profiles, both alone and in combination therapies. It has a number of pharmacological properties that distinguish it from other ARBs—the longest plasma half-life, highest lipophilicity and strongest receptor binding affinity in class. Telmisartan is, therefore has a broad indication for CV risk reduction in patients with atherothrombotic disease or diabetes mellitus (DM) with end-organ damage [5]. Telmisartan can effectively improve insulin sensitivity in patients with hypertension and because of its additive PPARγ agonistic action, it can improve