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Review

The vasoprotective axes of the renin-angiotensin system: Physiological relevance and therapeutic implications in cardiovascular, hypertensive and kidney diseases

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ABSTRACT

The renin-angiotensin system (RAS) is undisputedly one of the most prominent endocrine (tissue-to-tissue), paracrine (cell-to-cell) and intracrine (intracellular/nuclear) vasoactive systems in the physiological regulation of neural, cardiovascular, blood pressure, and kidney function. The importance of the RAS in the development and pathogenesis of cardiovascular, hypertensive and kidney diseases has now been firmly established in clinical trials and practice using renin inhibitors, angiotensin-converting enzyme (ACE) inhibitors, type 1 (AT_1) angiotensin II (ANG II) receptor blockers (ARBs), or aldosterone receptor antagonists as major therapeutic drugs. The major mechanisms of actions for these RAS inhibitors or receptor blockers are mediated primarily by blocking the detrimental effects of the classic angiotensinogen/renin/ACE/ANG II/AT_1/aldosterone axis. However, the RAS has expanded from this classic axis to include several other complex biochemical and physiological axes, which are derived from the metabolism of this classic axis. Currently, at least five axes of the RAS have been described, with each having its key substrate, enzyme, effector peptide, receptor, and/or downstream signaling pathways. These include the classic angiotensinogen/renin/ACE/ANG II/AT_1 receptor, the ANG II/APA/ANG III/AT_2/NO/cGMP, the ANG I/ANG II/ACE2/ANG (1–7)/*Mas* receptor, the prorenin/renin/prorenin receptor (PRR or Atp6ap2)/MAP kinases ERK1/2/V-ATPase, and the ANG III/APN/ANG IV/IRAP/AT_4 receptor axes. Since the roles and therapeutic implications of the classic angiotensinogen/renin/ACE/ANG II/AT_1 receptor axis have been extensively reviewed, this article will focus primarily on reviewing the roles and therapeutic implications of the vasoprotective axes of the RAS in cardiovascular, hypertensive and kidney diseases.

Contents

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1. Introduction

The renin-angiotensin system (RAS) is undisputedly one of the most important endocrine (tissue-to-tissue), paracrine (cell-to-cell) and intracrine (intracellular/nuclear) vasoactive systems in the physiological regulation of cardiovascular, blood pressure, and kidney function, and the development of cardiovascular, hypertensive, and renal diseases [1–5]. The discovery of each of key members of the RAS, uncovering their cardiovascular, blood pressure, and renal actions, and developing pharmacological drugs to target the key enzyme(s) and receptor(s) of the RAS to treat cardiovascular, hypertensive and renal diseases have become a successful story in the cardiovascular, hypertensive, and renal research [1–5]. The earliest and most significant member of the RAS, the rate-limiting enzyme renin, was first discovered by Tigerstedt and Bergman at Karolinska Institute in 1898 [6]. The foremost contribution of Tigerstedt and Bergman to the RAS research was their discovery of renin as a pressor substance released from the kidney, which increased blood pressure systemically [6]. However, it took almost 40 years until 1934, when Harry Goldblatt demonstrated in a landmark study that a vasopressor substance from the kidney induced hypertension in a dog model of two-kidney, one-clip (2K1C) renovascular hypertension [7]. Subsequent studies suggested that renal ischemia not only caused the release of renin from the kidney, but also a heat-stable, short-lived plasma pressor substance, which was initially named angiotonin or hypertensin, but was later widely recognized as angiotensinogen [8–10]. The liver was then considered to be the primary source of plasma angiotensinogen, with the first twelve amino acids, Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-. . ., being the most important for its biological activity. It was in early 1950s that Skeggs and colleagues purified this peptide and found that there were actually two peptides, termed angiotensin I (ANG I) with ten amino acids, Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu, and ANG II with eight amino acids, Asp-Arg-Val-Tyr-Ile-His-Pro-Phe, and that ANG I had to be cleaved to form ANG II to be active by angiotensin-converting enzyme (ACE) [11,12]. Interestingly, ACE is also known as Kininase II [13,14], which metabolizes the vasodepressor peptide bradykinin; thus ACE is not only responsible for ANG II formation, but also for degradation of bradykinin [14]. Therefore the RAS and the kinin-kallikrein-bradykinin system interact to regulate cardiovascular, blood pressure, and renal function in health and disease [15,16].

In the tissues which express an enzyme named aminopeptidase A (APA), especially in the kidney, ANG II is metabolized to form des-aspartyl[1]-ANG II, also termed ANG III with seven amino acids, Arg-Val-Tyr-Ile-His-Pro-Phe [17–19]. ANG III is further metabolized by the action of Aminopeptidase N (APN) to form ANG IV with six amino acids, Val-Tyr-Ile-His-Pro-Phe, ANG (3–8) [17,19,20]. Unlike ANG II, both ANG III and ANG IV were previously considered partial agonists for ANG II receptors with lesser vasopressor activity [21–23]. More recently, ANG III has been recognized as a major ligand for the AT_2 receptor/NO/cGMP signaling cascade [18,24,25], whereas ANG IV is thought to activate the AT_4 receptor [23,26–28]. In late 1980s and early 1990s, through the study of ANG II receptor pharmacology it was discovered that ANG II acted on at least two different classes of G protein-coupled receptors, which led to the development of two classes of nonpeptide ANG II receptor antagonists, losartan as a representative blocker for type 1 (AT_1) and PD123319 as a representative type 2 (AT_2) receptor blockers [1,29–31]. The AT_1 receptor was successfully cloned in 1991 by Murphy et al. [32] and Sasaki et al. [33], respectively, which shares the seven-transmembrane-region motif with the G protein-coupled receptor superfamily. The AT_1 receptor mediates the well-recognized effects of ANG II on cardiovascular, blood pressure, and renal systems, such as vasopressor, cardiac hypertrophic, hypertensive, renal vasoactive and salt-retaining actions, as well as aldosterone biosynthesis and release [1,5,29,31]. The AT_2 receptor was successfully cloned by Mukoyama et al. [34], Nakajima et al. [35], and Kambayashi et al. [36], respectively. The cloned AT_2 receptor has 34% identical sequence to the cloned AT_1 receptor, shares a seven-transmembrane domain topology [34], and appears to mediate ANG II-induced inhibition of protein tyrosine phosphatase in COS-7 cells [36]. The 3rd ANG receptor termed "AT_3" was reportedly cloned to encode a Mr 40,959 protein with 95% amino acid identity to the rat smooth muscle AT_1 receptor, which also mediates ANG II-induced Ca^{2+} mobilization [37]. However, the so-called "AT_3" receptor has not been recognized in the field. The 4th ANG receptor was identified in 2001 as insulin-regulated aminopeptidase (IRAP) by Albiston et al. using protein purification and peptide sequencing [26]. ANG (3–8) was found to bind and activate this receptor in the brain and plays an important role in learning and memory [26,38]. Most recently, the *Mas* oncogene was identified by Santos et al. as the specific receptor for ANG (1–7) [39], playing a key role in mediating ANG (1–7)-induced cardiovascular, vasodepressor, and renal responses [39–42].

Collectively, it is now well understood that the classic RAS axis includes the substrate angiotensinogen primarily from the liver, which is cleaved by the rate-limiting enzyme renin released primarily from the juxtaglomerulus apparatus (JGA) of the kidney to form the biologically inactive ANG I. ACE, which is primarily