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Review

A century old renin–angiotensin system still grows with endless possibilities: AT_1 receptor signaling cascades in cardiovascular physiopathology

Pitchai Balakumar [a,*], Gowraganahalli Jagadeesh [b,1]

[a] Pharmacology Unit, Faculty of Pharmacy, AIMST University, Semeling, 08100 Bedong, Kedah Darul Aman, Malaysia
[b] Division of Cardiovascular and Renal Products, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD 20993, USA

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ABSTRACT

Ang II, the primary effector pleiotropic hormone of the renin–angiotensin system (RAS) cascade, mediates physiological control of blood pressure and electrolyte balance through its action on vascular tone, aldosterone secretion, renal sodium absorption, water intake, sympathetic activity and vasopressin release. It affects the function of most of the organs far beyond blood pressure control including heart, blood vessels, kidney and brain, thus, causing both beneficial and deleterious effects. However, the protective axis of the RAS composed of ACE2, Ang (1–7), alamandine, and Mas and MargD receptors might oppose some harmful effects of Ang II and might promote beneficial cardiovascular effects. Newly identified RAS family peptides, Ang A and angioprotectin, further extend the complexities in understanding the cardiovascular physiopathology of RAS. Most of the diverse actions of Ang II are mediated by AT_1 receptors, which couple to classical Gq/11 protein and activate multiple downstream signals, including PKC, ERK1/2, Raf, tyrosine kinases, receptor tyrosine kinases (EGFR, PDGF, insulin receptor), nuclear factor κB and reactive oxygen species (ROS). Receptor activation via G12/13 stimulates Rho-kinase, which causes vascular contraction and hypertrophy. The AT_1 receptor activation also stimulates G protein-independent signaling pathways such as β-arrestin-mediated MAPK activation and Src-JAK/STAT. AT_1 receptor-mediated activation of NADPH oxidase releases ROS, resulting in the activation of pro-inflammatory transcription factors and stimulation of small G proteins such as Ras, Rac and RhoA. The components of the RAS and the major Ang II-induced signaling cascades of AT_1 receptors are reviewed.

Contents

Abbreviations: RAS, renin–angiotensin system; AOG, angiotensinogen; Ang II, angiotensin II; ACE, angiotensin converting enzyme; ARBs, angiotensin AT_1 receptor blockers; Mas R, Mas receptor; TGF-β, transforming growth factor-β; Ang A, angiotensin A; eNOS, endothelial nitric oxide synthase; MrgD, a novel receptor of alamandine; PRR, (pro)renin receptor; ERK 1/2, p42/p44 mitogen-activated protein kinase or extracellular signal-regulated protein kinases 1 and 2; PAI-1, plasminogen activator inhibitor-1; TNFα, tumor necrosis factor α; PMZF, promyelocytic zinc finger; v-H(+)-ATPase, vacuolar-H(+)-ATPase; GPCRs, G protein-coupled receptors; PLC, phospholipase C; PLA2, phospholipase A2; PLD, phospholipase D; DAG, diacylglycerol; PKC, protein kinase C; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; ROS, reactive oxygen species; GRKs, G protein-coupled receptor kinases; RGS, regulators of G protein signaling; PIP2, phosphatidylinositol-4,5-bisphosphate; IP_3, inositol trisphosphate; IP_4, inositol tetrakisphosphate; MLCK, myosin light chain kinase; VSMCs, vascular smooth muscle cells; MLCP, myosin light chain phosphatase; DGK, diacylglycerol kinase; EGFR, epidermal growth factor receptor; ADAM17, A Disintegrin And Metalloprotease 17; PDGFR, platelet-derived growth factor receptor; PC, phosphatidylcholine; PA, phosphatidic acid; phox, phagocytic oxidase; JAK, janus kinase; STAT, signal transducer and activators of transcription.

* Correspondence author at: Associate Professor of Pharmacology and Head, Pharmacology Unit, Faculty of Pharmacy, AIMST University, Semeling, 08100 Bedong, Kedah Darul Aman, Malaysia. Tel.: +60 44298000x1280.
E-mail addresses: pbala2006@gmail.com (P. Balakumar), Gowra.Jagadeesh@fda.hhs.gov, jagadeesh49@yahoo.com (G. Jagadeesh).

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1. Introduction

The renin–angiotensin system (RAS) functions as an endocrine system to play a key role in cardiovascular and renal physiology. Its overactivation is implicated in the induction and progression of hypertension, atherosclerosis, cardiac hypertrophy, heart failure, ischemic heart disease, and renovascular disorders [1–5]. Angiotensin II (Ang II), the principal component of the RAS cascade, has diverse physiological actions regulating blood pressure and salt/water balance through a variety of effects that affects the function of most of the organs including heart, kidney, adrenal gland, vasculature and central nervous system. Chronic stimulation or overactivation produces deleterious effects on cardiovascular and renal function [2,3].

In 1898, Tigerstedt and Bergman at the Karolinska Institute reported the pressor effect of rabbit renal tissue extracts and named the substance renin, because it was extracted from kidneys [6]. In 1934, Harry Goldblatt induced hypertension in dogs by clamping the renal artery [7]. Soon after this event, scientists in the Medical School of the University of Buenos Aires, Argentina, and in the Eli-Lilly Laboratories at Indianapolis, USA, employed the Goldblatt technique and demonstrated renal secretion of a pressor agent similar to that of renin. Both teams described the presence of a novel compound in the renal vein blood of the ischemic kidney that had a short pressor effect. The researchers at the Buenos Aires called the compound 'hypertensin', whereas at the Eli-Lilly Lab it was called 'angiotonin'. In 1958, Page and Braun-Menéndez combined both terms (*angio*tonin and hyper*tensin*) and agreed to use a name derived from half of each original name, '*angiotensin*' [8,9]. Since then several components of RAS have been identified that play physiopathological role in cardiovascular and renal systems. The selected discoveries of RAS components and their target receptors are summarized in Table 1.

Ang II exerts its effects by binding to receptors in target tissues or organs. Two major subtypes of Ang II receptors, AT_1 and AT_2 were identified by selective ligands and were later characterized as G protein-coupled receptors. Site directed mutagenesis and molecular-dynamics simulation studies have identified the specific amino acids on Ang II and the type of binding interactions with the receptor determinants for ligand binding activation and signal transduction. On the receptor, the extracellular loops and the transmembrane domains are involved in defining the agonistic activity of Ang II. G protein interaction occurs on the transmembrane domain at the amino terminus and the cytoplasmic domains of the 2nd and 3rd intracellular loops [192]. The carboxy terminal tail of the receptor contains numerous serine and threonine residues that are probable sites for phosphorylation by G protein receptor kinases. Phosphorylation negates further G protein stimulation and simultaneously recruits β-arrestins that initiate receptor internalization [10–12]. The β-arrestin-scaffolded signaling mediates 'secondary signaling' involving multiples kinases that link to cytoprotective downstream signaling molecules. The selective G protein-independent signaling has led to the development of 'biased agonists' that activate G protein-independent signaling while blocking the detrimental actions on G protein activation, thus, demonstrating their role in cardiovascular diseases. Additionally, Ang II through AT_1 receptors stimulates multiple signaling pathways, crosstalk with several tyrosine kinases, and transactivates growth factor receptors. This review focuses on recent advances in understanding the cardiovascular

Table 1
Selected discoveries of RAS components.

S. no.	Major findings	Year	Reference
1	Discovery of Ang I, Ang II and ACE (These were previously called as hypertensin I, hypertensin II and hypertensin-converting enzyme, respectively)	1956	[176]
2	Synthesis and pharmacology of angiotonin (Ang II)	1957	[177]
3	Since *angio*tonin and hyper*tensin* were considered as the same substance, Page and Braun-Menéndez agreed on the hybrid term '*angiotensin*'	1958	[8]
4	Historical development of saralasin	1970–1980	[178]
5	Lin and Goodfriend identified angiotensin receptors	1970	[179]
6	Teprotide, a nonapeptide isolated from the snake *Bothrops jararaca*, was identified as an angiotensin converting enzyme inhibitor that potentiated the actions of bradykinin.	1965–1970	[180–182]
7	Captopril, the first orally active ACE inhibitor, was synthesized by Miguel Ondetti et al.	1977	[183]
8	Approval of captopril by the US FDA for the treatment of hypertension	1981	[184]
9	Non-peptide orally active AT_1 receptor blockers were developed	1982–1990	[1,185]
10	A committee of the International Society for Hypertension, The American Heart Association, and the World Health Organization proposed abbreviating angiotensin to Ang	1987	[186]
11	Ang (1–7) has cellular functions that differ from those established for Ang II.	1991	[187]
12	Approval of losartan, the first AT_1 receptor antagonist, by the US FDA for the treatment of hypertension.	1995	[188]
13	Discovery of ACE2 converting Ang I to Ang 1–9 by Donoghue et al.	2000	[14]
14	The (pro)renin receptor was discovered by Nguyen et al.	2002	[51]
15	Proangiotensin-12 was identified and suggested to be a component of the tissue RAS	2006	[189]
16	Approval of aliskiren, the first orally active renin inhibitor, by the US FDA for the management of hypertension	2007	[190]
17	Approval of azilsartan, the eighth AT_1 receptor blocker, for the management of hypertension	2011	[191]