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AT1 receptor signaling pathways in the cardiovascular system

Tatsuo Kawai[1], **Steven J Forrester**[1], **Shannon O'Brien**[1,2], **Ariele Baggett**[1], **Victor Rizzo**[1], and **Satoru Eguchi**[1,*]

[1]Cardiovascular Research Center, Lewis Katz School of Medicine, Temple University, 3500 N. Broad Street, Philadelphia, PA 19140, USA

[2]School of Biomedical Sciences, The University of Queensland, St. Lucia, Queensland 4072, Australia

Abstract

The importance of the renin angiotensin aldosterone system in cardiovascular physiology and pathophysiology has been well described whereas the detailed molecular mechanisms remain elusive. The angiotensin II type 1 receptor (AT1 receptor) is one of the key players in the renin angiotensin aldosterone system. The AT1 receptor promotes various intracellular signaling pathways resulting in hypertension, endothelial dysfunction, vascular remodeling and end organ damage. Accumulating evidence shows the complex picture of AT1 receptor-mediated signaling; AT1 receptor-mediated heterotrimeric G protein-dependent signaling, transactivation of growth factor receptors, NADPH oxidase and ROS signaling, G protein-independent signaling, including the β-arrestin signals and interaction with several AT1 receptor interacting proteins. In addition, there is functional cross-talk between the AT1 receptor signaling pathway and other signaling pathways. In this review, we will summarize an up to date overview of essential AT1 receptor signaling events and their functional significances in the cardiovascular system.

Keywords

angiotensin II; signal transduction; vascular smooth muscle cell; endothelial cell; ADAM17; EGF receptor

1. Introduction

The Renin-angiotensin-aldosterone system (RAAS) plays an integral role in cardiovascular and renal physiology and pathophysiology, exerting direct autocrine and paracrine as well as endocrine effects. The system influences a large range of homeostatic and modulatory

*Corresponding author at: Cardiovascular Research Center, Lewis Katz School of Medicine, Temple University, 3500 N. Broad Street, Philadelphia, PA 19140, USA, seguchi@temple.edu.

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processes including regulation of salt and water balance, vasoconstriction, cell/tissue remodeling and dysfunction in the cardiovascular system. Angiotensin (AngII), the major bioactive peptide of the RAAS, mediates many of its effects by binding to two major G protein-coupled receptors (GPCRs): AngII type 1 receptor (AT1 receptor) and the AngII type 2 receptor (AT2 receptor) (1). Although the AT2 receptor is thought to oppose the effects of the AT1 receptor, many of the effects of AngII are mediated through the activation of the AT1 receptor. The AT1 receptor is predominantly expressed in various tissues throughout the cardiovascular system including vascular smooth muscle, endothelium, heart and kidney. The AT1 receptor promotes intracellular signaling pathways through the activation of various protein kinases, subunits of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, growth factor receptor transactivation (1–5), or direct interactions with AT1 receptor interacting proteins such as Janus kinase 2 (JAK2), phospholipase C (PLC) γ1, AT1 receptor associated protein (ATRAP), type 1 angiotensin II receptor-associated protein (ARAP1) and Guanine nucleotide exchange factor (GEF)-like protein (GLP) (1, 2, 6, 7).

Although the physiological/pathophysiological roles of the AT2 receptor have not been fully elucidated, there is an increasing interest in AT2 receptor functions in the cardiovascular system (8–10). AT2 receptor stimulation causes vasorelaxation through protein kinase A (PKA)-dependent endothelial nitric oxide (NO) synthase (eNOS) activation or paracrine signaling induced by bradykinin/NO/cyclic GMP production (1, 8). Mice overexpressing the AT2 receptor exhibit vasodilation (11), and pharmacological stimulation of AT2 receptor promotes natriuresis, lowering of blood pressure, and inhibits AngII-mediated hypertension (12, 13). In systemic AT2 receptor transgenic mice with AngII infusion, perivascular fibrosis but not cardiac hypertrophy is attenuated compared with wild-type mice (14). By contrast, AT2 receptor stimulation (candesartan plus AngII) promotes vasoconstriction in isolated mesenteric arteries from spontaneously hypertensive rats (15). Mice with ventricular specific AT2 receptor overexpression develop dilated cardiomyopathy and heart failure (16). These confusing results regarding AT2 receptor function is suggested to be largely dependent on expression levels of AT2 receptor in addition to Nox2 regulation and transforming growth factor beta 1 (TGFβ1) signaling pathways (17). The AT2 receptor will not be discussed further in this review, however, there are excellent review articles summarizing recent findings regarding the role of AT2 receptor in hypertension, vascular remodeling and cardiovascular dysfunction (9, 10, 18).

Angiotensin-1-7 (Ang1-7) is converted by angiotensin converting enzyme 2 (ACE2) and is thought to balance the RAAS system by promoting an antagonistic effect on the responses elicited by AngII such as vasodilation (19, 20). Ang1-7 exerts its effects through the Mas receptor. The Ang1-7 activation of Mas receptor contributes to NO production through eNOS Ser1177 phosphorylation (21). However, Ang1-7 attenuates cardiac hypertrophy and fibrosis induced by AngII independent of alterations in blood pressure (22). While the Mas receptor is a GPCR, its G protein coupling is controversial and Mas may also signal G protein independently or constitutively without ligand binding (1). Please note that detailed review articles focused on Ang1-7/Mas functions and mechanisms have been published, whereas more emphasis is needed regarding Mas signaling and how it interacts with AT1 receptor signal transduction (19, 20).

The AT1 receptor is widely expressed in various tissues such as heart, kidney, adrenal gland, brain and adipose tissues (23), with these systems in turn affecting the cardiovascular system directly or indirectly via circulatory as well as local/tissue RAAS (24–26). This review will outline recent findings regarding the AT1 receptor signaling pathways in the cardiovascular system, highlighting its influence on vascular smooth muscle cells (VSMC) and endothelial cells (EC) functions.

2. AT1 receptor signaling in the cardiovascular system

AngII mediates AT1 receptor activation via stacking interactions between Phe^{8}(AngII)/His^{256}(AT1 receptor) and Tyr^{4}(AngII)/Asn^{111}(AT1 receptor) (1), resulting in a conformational change in transmembrane (TM)3-TM6 helices and interaction between TM2 and TM7 (27). Upon AngII binding, the AT1 receptor facilitates a variety of cytoplasmic signaling pathways that mediate VSMC remodeling including hypertrophy and migration. The AT1 receptor interacts with heterotrimeric G-proteins ($G_{q/11}$, G_i, G_{12} and G_{13}) which transduce signals to the cognate effectors and downstream second messengers including PLCβ and Rho GEFs, and inositol triphosphate, diacylglycerol and reactive oxygen species (ROS), respectively. This in turn regulates VSMCs contraction via activation of myosin light chain kinase (MLCK) or inhibition of myosin light chain phosphatase (MLCP) (2, 28, 29). Src family kinases also regulate vascular contraction via MLCP, attenuating myosin light chain phosphorylation and contraction in AngII infused mice (30). AngII-dependent hypertension, but not vascular remodeling, is attenuated in c-Src+/− mice (31). Similarly, Ras-related protein 1 (Rap1b) knockdown or PDZ-RhoGEF/RhoA/Rho kinase signaling cascade promotes vascular contraction induced by AngII through inhibition of MLCP (32, 33). The AT1 receptor has also been shown to regulate vasoconstriction through phosphorylation of with-no-lysine (WNK) and Ste20/SPS1-related proline/alanine-rich kinase (SPAK) and subsequent modulation of Na-K-Cl cotransporter isoform 1 (NKCC1) (34). In addition, calcium activated chloride channel anoctamin-1 (ANO1) is induced by AngII via AT1 receptor-phosphatidylinositol 3-kinase (PI3K)/AKT pathway and regulates vasoconstriction (35), with VSMC specific ANO1 knockdown attenuating AngII-induced contractile responses (36).

AT1 receptor expressed in the cardiovascular system has been shown to activate a variety of intracellular protein kinases including mitogen-activated protein kinase (MAPK) family [extracellular signal regulated kinase (ERK), c-Jun N terminal kinase (JNK), p38MAPK], p70 S6 kinase, AKT/protein kinase B(PKB), various protein kinase C (PKC) isoforms, receptor and non-receptor tyrosine kinases and serine/threonine kinases (2, 28, 37–40). These kinases are believed to stimulate NADPH oxidase, ROS generation and protein synthesis, causing hypertrophy, hyperplasia and migration of VSMCs (2, 41–45), cardiac hypertrophy (46) and renal deterioration (47).

3. Growth factor receptor transactivation

Activation of the AT1 receptor can transactivate receptor tyrosine kinases, thereby enabling AngII to regulate a multitude of signaling pathways downstream of growth factor receptors. Transactivation of the epidermal growth factor (EGF) receptor (EGFR), the major model of

AT1 receptor 'cross-talk,' drives cellular process distal to the EGFR (5) (Figure 1). AngII stimulation causes rapid activation of the EGFR and subsequent activation of Ras/ERK cascade and various intracellular signaling such as the AKT/p70 S6 kinase cascade and endoplasmic reticulum (ER) stress/unfolded protein response (5). Upon activation of the AT1 receptor, second messengers such as Ca^{2+} and ROS mediate activation of A Disintegrin And Metalloproteinase 17 (ADAM17) (2, 5). Activation of transmembrane ADAM17 leads to the cleavage of inactive membrane-bound precursors and the production of their complementary active form (Heparin-binding EGF-like growth factor (HB-EGF), neuregulin, EGF, etc). Although some reports show G_q-independent EGFR transactivation (48, 49), ADAM17-mediated HB-EGF shedding by AngII requires G_q activation (45, 50) and subsequent ADAM17 Tyr^{702} phosphorylation (51–53). The ADAM17-dependent EGFR transactivation causes hypertrophy and migration of VSMCs through the Ras/ERK pathway and the PI3K/Akt/mechanistic target of rapamycin (mTOR)/p70S6K/eukaryotic translation initiation factor 4E (eIF4E) pathway (51–53). In addition, BMX (bone marrow kinase), CHKA (choline kinase alpha) and TRIO [triple functional domain (PTPRF interacting)] have been identified as upstream signaling molecules required for AngII-induced EGFR transactivation by siRNA library screening (54). In ECs, AT1 receptor-mediated EGFR transactivation promotes cell migration via focal adhesion kinase and paxillin phosphorylation (55). It also promotes release of microparticles from ECs, resulting in inflammatory activation (56). Furthermore, systemic inhibition of ADAM17, EGFR or ER stress attenuates aortic wall thickening induced by AngII (57, 58), suggestive of a role for AT1 receptor-EGFR transactivation in cardiovascular pathology (5).

AngII also leads to activation of the platelet-derived growth factor receptor (PDGFR) in cardiovascular tissue (59, 60), mediating ERK activation (61), and regulating vascular hypertrophy and fibrosis (62, 63). A lot less is known in regard to the physiological significance of the Insulin-like growth factor-1 receptor (IGF-1R) transactivation induced by AngII in VSMCs (64). IGF-1R transactivation is Src-dependent, and is required for PI3K and p70 S6 kinase activation by AngII, but not for ERK stimulation (65). IGF-1R transactivation is important for Src kinase mediated cortactin phosphorylation and cytoskeletal reorganization in response to AngII (66). ROS production by AngII is suggested to depend partially on IGF-1R transactivation, leading to p38MAPK and ERK5 activation in VSMCs (67). However, unlike the EGFR, the picture is not as complete, with little information about the role of transactivation of PDGFR and IGF-1R in cardiovascular pathophysiology.

4. Small G proteins activated by AT1 receptor

AngII activates various small G proteins including Ras, Rho and Rac, potentially regulating vascular remodeling (68). GTP-bound RhoA and RhoA in the particulate fraction is upregulated by AngII in VSMCs (69, 70). G12/13 mediates RhoA activation induced by AngII, and this regulation is independent of $G_{q/11}$ signaling stimulated by AngII (71, 72). Cardiac specific G_{13} deficient mouse is protected from AngII-induced cardiac hypertrophy and fibrosis (71). Moreover, the Rho/Rho-associated protein kinase (ROCK) pathway is also important in vascular remodeling (68) and cardiovascular diseases (73–75). We have previously shown that a tyrosine kinase, PYK2, and its upstream activation by PKCδ is

essential for AngII-induced Rho/ROCK pathway activation in VSMCs, and this is in parallel with EGFR transactivation pathways in VSMCs (76). Activation of Rho/ROCK is also required for JNK activation and subsequent VSMCs migration (76). Alternatively, AngII promotes Jak2-dependent Arhgef1 phosphorylation, resulting in RhoA activation and subsequent blood pressure elevation (77, 78). In addition, RhoA activation mediates nuclear factor kB (NF-kB) activation and subsequent IL-6 expression in VSMCs (79). ROCK inhibitor suppresses the expression of monocyte chemoattractant protein-1 (MCP-1) or plasminogen activator inhibitor-1 (PAI-1) induced by AngII in VSMCs (80, 81). Taken together, RhoA/ROCK appears essential in the vascular contraction, remodeling as well as inflammation induced by AngII (Figure 2). Rac activates p21-activated kinase 1 (PAK1) in VSMCs, resulting in JNK activation and VSMC hypertrophy (82–84) as well as promoting ROS production in VSMCs (85).

5. NADPH oxidase subunits and ROS

Various NADPH oxidase subunits including Nox1, p22 phox, p47 phox and p67 phox, are stimulated via AT1 receptor activation. This produces H_2O_2 and superoxide (3, 4) and results in the stimulation of p38MAPK/AKT pathway and protein synthesis (28). In ECs, AT1 receptor signaling mediates endothelial dysfunction via inhibition of NO production and induction of vascular insulin resistance (86, 87). The role of AngII-induced oxidative stress in the pathogenesis of endothelial dysfunction has also been validated with AT1 receptor antagonists (88, 89). Acute AngII stimulation of AT1 receptor increases NO production via eNOS phosphorylation (63, 90–92) and eNOS gene transfer inhibits VSMC hypertrophy induced by AngII (63). However, AngII infusion or endothelial NADPH oxidase-derived H_2O_2 induced by AngII also causes eNOS uncoupling and superoxide production (90, 93, 94). AngII also activates poly (ADP-ribose) polymerase (PARP), resulting in a decrease in intracellular NAD+, ATP levels and EC dysfunction (95). Deficiency of p47 phox in mice ablates enhanced medial thickness of the aorta induced by AngII infusion (96). AngII-induced hypertension and vascular remodeling are exaggerated in superoxide dismutase 1 (SOD1) knockout mice, whereas these responses are reduced in SOD1 transgenic mice (97). In contrast, AngII-induced hypertension is unaltered in NOX2 deficient mice, while vascular remodeling is attenuated in cerebral arterioles (98). These results suggest that AT1 receptor mediates endothelial dysfunction and vascular remodeling by vascular ROS production which likely includes peroxynitrite generation.

6. AT1 receptor interacting proteins

β-arrestin, initially discovered to mediate desensitization and subsequent uncoupling of activated AT1 receptor with associated G proteins, also serves as a signaling system. GPCR kinases (GRK) phosphorylate activated GPCRs, enabling β-arrestin to bind to the receptor, terminate further G protein-mediated signaling and target the receptor for internalization (99). Binding of β-arrestin 2 to the AT1 receptor is essential for ERK1/2 and Akt activation stimulating protein synthesis through Akt-mTOR-p70/85S6K and ERK1/2-p90RSK pathways in VSMCs (100, 101). In addition, mechanical stretch facilitates β-arrestin 2-biased pro-survival signaling through AT1 receptor mediated EGFR transactivation in AngII- or G protein-independent manner in cardiac myocytes (102). Thus, β-arrestin-biased

AT1 receptor agonists have been created in attempts to treat heart failure (103–105). There are conflicting studies suggesting both benefit and harm of β-arrestin signals in cardiovascular hypertrophy or heart failure. It appears that β-arrestin 2 inhibition and/or β-arrestin 1 stimulation might be desirable for the treatment of VSMC hypertrophy, hyperplasia and atherosclerosis, contrary to cardiac hypertrophy and heart failure, for which β-arrestin 2 stimulation appears to be a potential therapeutic strategy. It is also important to note the role of β-arrestin 1 in mediating ERK1/2-dependent aldosterone production and secretion induced by adrenal AT1 receptor stimulation (106). Inhibition of adrenal β-arrestin 1 may be beneficial in heart failure. This mechanism may also explain aldosterone escape seen in certain patients treated with AT1 receptor blockers (107). Currently utilized AT1 receptor blockers have been classified as dual G protein/β-arrestin 1 inhibitors or G protein selective inhibitors (108).

AT1 receptor forms heterodimer with other GPCRs (α_{1D} adrenergic receptor, β_1 adrenergic receptor, β_2 adrenergic receptor, bradykinin receptor B_2, dopamin receptor D_1, prostaglandin F receptor, and P2Y purinergic receptor 6) (109–114) in addition to other receptors including the lectin-like oxidized low density lipoprotein receptor oxLDL receptor (115) and EGFR (116). An altered interaction between AT1 receptor and these receptors is suggested to affect physiological/pathophysiological conditions such as vasoconstriction, hypertension, atherosclerosis or impaired sodium excretion.

The AT1 receptor also interacts directly with various other proteins (2, 6). The C-terminal cytoplasmic domain of AT1 receptor is an important feature of AT1 receptor structure and regulation, known to interact with JAK2 and PLCγ1 (117, 118). AT1 interaction is necessary for AngII-induced JAK2 activation. Both JAK2 and PLCγ1 share the YIPP motif binding site at the C terminus of the AT1 receptor. As mentioned, this JAK2 activation contributes to AngII-induced vasoconstriction (77, 78). Except for contribution to inositol 1,4,5-trisphosphate production, functional significance of PLCγ1 activation by AngII remains obscure (117, 118). ATRAP, a three-transmembrane protein, binds to the C-terminal cytoplasmic domain, regulating AT1 receptor internalization in VSMCs (119) and cardiac myocytes (120) in addition to negatively modulating AT1 receptor-induced signal transduction (121, 122). ATRAP attenuates AT1 receptor-mediated vascular senescence via calcineurin/Nuclear factor of activated T-cells (NFAT) pathway (123). ATRAP transgenic mice did not reveal a significant phenotype but neo-intimal formation induced by vascular injury was inhibited and ERK, STAT1 and STAT3 activity was attenuated (124). Similarly, in cardiac specific ATRAP transgenic mice, cardiac hypertrophy induced by AngII infusion is attenuated (125). ARAP1 also binds to AT1 receptor and regulates AT1 receptor recycling to the plasma membrane (126). Proximal tubules-specific ARAP1 transgenic mice show hypertension and kidney hypertrophy through enhancement of AT1 signaling (127). Overexpression of GLP, a cytosolic protein, causes hypertrophy in VSMCs and renal proximal tubular cells via, at least in part, activation of Akt and inhibition of p28kip1 protein expression (128).

Gamma-aminobutyric acid (GABA) receptor-associated protein (GABARAP), a protein involved in the trafficking of intracellular GABA(A) receptor through microtubule networks, interacts with C-terminal domain of AT1 receptor and enhances the trafficking of AT1

receptor to the plasma membrane (129). Tubulin directly binds to the AT1 receptor, regulating AT1 receptor trafficking from the ER to the cell surface (130). AT1 receptor also directly binds to filamin A, an actin cross-linking protein, with agonist activation of the AT1 receptor promoting filamin phosphorylation, suggestive of a direct role of AT1 receptor in actin remodeling mediated by filamin (131). β-COP (Coatomer subunit β), a component of Coat Protein I (COPI) transport vesicles involved in the transport between different Golgi stacks and transport from the Golgi to the ER, interacts with AT1 receptor on Lys308 and regulates AT1 receptor export trafficking to the cell surface (132). Taken together, AT1 receptor binds to various interacting proteins through C-terminal domain and facilitates diverse signaling including AT1 receptor trafficking and cell surface expression (Table 1).

7. Cascades of Wnt, Notch, Hippo and mitochondria

In addition, there is functional crosstalk between AT1 signaling pathway and other signaling pathways. AngII upregulates receptor activator of nuclear factor-κB (RANKL) system in VSMCs, with AT1 receptor blockade attenuating RANKL expression and vascular calcification (133). Wnt/β-catenin pathway has an important role in embryonic development, tissue regeneration, cell proliferation and migration. AngII-induced β-catenin signaling pathway activation was suppressed by a nuclear orphan receptor, Nur77. Nur77 negatively regulates AngII-induced VSMC proliferation and migration by promoting β-catenin degradation and inhibition of its transcriptional activity (134). Animal models suggest β-catenin is required for adaptive cardiac remodeling by AngII infusion (135). A pro-growth factor, Wnt1 inducible signaling pathway protein 1 (WISP1), is a target of TCF/LEF (T-cell factor/lymphoid enhancer factor) and promotes cardiac hypertrophy. AT1 receptor physical association with Nox2 is further enhanced following AngII stimulation, mediating WISP1 induction and cardiomyocyte hypertrophy (136). Similarly, Wnt/β-catenin pathway is suggested to be involved in AngII-induced renal injury and renal fibrosis (137, 138). AngII enhances Wnt1 expression, β-catenin nuclear translocation in mouse podocytes, with inhibition of Wnt/β-catenin pathway attenuating podocyte injury (139). β-catenin destabilization reagent also inhibits AngII-induced β-catenin, collagen I, fibronectin and osteopontin in mouse collecting duct cell or kidney of renovascular hypertensive rat (140, 141). Thus, there is accumulating evidence indicating a close relationship between the Wnt/β-catenin pathway and AT1 receptor in regard to cardiovascular remodeling and chronic kidney diseases.

Notch signaling pathway, a regulator of cell fate in the developing heart, is also implicated in cardiovascular pathophysiology (142). AT1 receptor stimulates Notch signaling pathway through an increase of γ-secretase enzymatic activity, mediating VSMCs proliferation and migration (143). Notch inhibition or γ-secretase complex silencing in mice attenuates hypertension induced by AngII (144, 145). Notch3 −/− mice show attenuated renal vascular constriction, vessel wall thickening and hypertension induced by AngII. In contrast, Notch3 −/− mice show enhanced cardiac hypertrophy, tubular dilation or fibrosis in kidney, and greater mortality due to heart failure induced by AngII. This is suggestive of a role of Notch3 in end organ adaptation in hypertension (146). In addition, activation of Notch1 signaling is observed in AngII-induced abdominal aortic aneurysm (AAA). AAA formation induced by AngII is attenuated by Notch1 haploinsufficiency via modulation of macrophage

infiltration or inflammatory activation (147). AngII-induced AAA formation and vascular inflammation is also attenuated by pharmacological inhibition of Notch signaling (148).

Hippo signaling pathway is a complex signaling network, regulating cell proliferation and apoptosis to control organ size, with recent studies revealing GPCRs serve as upstream regulators of the Hippo pathway (149). AngII binding to AT1 receptor inhibits Hippo signaling by decreasing the activity of the large tumor suppressor kinase (LATS), leading to nuclear translocation of Yes-associated protein (YAP) in HEK293T cells. In contrast, AngII does not affect Hippo pathway activity in podocytes (150). Altogether, recent studies reveal various crosstalk between the AT1 receptor signaling pathways and other signaling pathways (Figure 3). Although not all of functional significance has been elucidated, they show new roles for AngII-mediated signaling mechanisms and cardiovascular pathophysiology.

AngII has been shown to induce mitochondrial dysfunction leading to mitochondrial ROS generation which modulates various AngII responses including experimental hypertension (151). Mitochondrial ROS production induced by AngII appears to require NADH/NADPH oxidase such as NOX2 in ECs (152). Pharmacological and genetic inhibition of mitochondrial ROS (152, 153) are effective in reducing AngII-induced hypertension and vascular dysfunction in rodents. AngII-induced hypertension and vascular dysfunction also involve mitochondrial ROS-dependent activation of the L-type Ca^{2+} channel in VSMCs (154). In addition, AngII induces mitochondrial fragmentation via dynamin-related protein 1 (Drp1) phosphorylation in VSMCs and neuroblastoma cells (155, 156). siRNA silencing of Drp1 attenuates AngII-induced ERK activation and matrix metalloproteinase 2/9 induction in VSMCs (155). Mitofusion 2 (MFN2), another GTPase, controls mitochondrial fusion. MFN2 over-expression attenuates AngII-induced cardiac myocyte hypertrophy in vitro and in vivo (157). These data suggest a presence of AngII-mediated mitochondrial signal transduction in regulating cardiovascular pathophysiology.

8. Tissue-specific roles of AT1 receptor and transcriptional factors

Recently, tissue specific knockouts of the AT1 receptor has enabled researchers to disassociate the effects of AT1 receptor signaling in a variety of tissues. AT1 receptor in VSMCs is essential for AngII-mediated regulation of renal blood flow, and mice with VSMC specific AT1 receptor depletion show increased urinary sodium excretion and attenuated AngII-induced high blood pressure (158). Mice with principal cell specific AT1 receptor depletion show enhanced natriuresis and a modest decrease in blood pressure in the initial phase of AngII-dependent hypertension (159). AT1 receptor depletion in VSMCs or ECs did not affect AngII-induced medial thickening, AAA formation and atherosclerosis (160, 161), however depletion of AT1 receptor in ECs attenuates thoracic aortic aneurysm (TAA) formation (162). Depletion in fibroblasts attenuated AngII-induced medial hyperplasia in the ascending aorta (161). These recent studies suggest the importance of tissue specific AT1 receptor signaling on hypertension and vascular remodeling.

Hypoxia-inducible factor 1 alpha (HIF-1α) and peroxisome proliferator-activated receptor gamma (PPARγ) are also considered to regulate AngII functions in tissue/cell type specifically. We have shown that AngII upregulates HIF-1α expression and induces

ADAM17 expression in VSMCs via transcriptional up-regulation (163). In addition, reduced medial wall thickening and hypertension induced by AngII is observed in VSMC specific HIF-1α knockout mice (164). However, VSMCs specific HIF-1α knockout mice are also reported to show increased AT1 receptor expression in vasculature and elevated blood pressure with downregulated PPARγ (165). It has been demonstrated that vascular smooth muscle-specific overexpression of a dominant negative human PPARγ mutation in mice (P467L) leads to increased angiotensin-II-dependent vasoconstriction (166) and enhanced VSMC ERK activation (167). Thus, PPARγ agonist inhibits AngII-induced PKCζ activation, ERK1/2 activation, Krueppel-like factor 5 expression and VSMC proliferation (168). In addition, enhanced AngII-induced vascular remodeling, contractility, inflammation and endothelial dysfunction are observed in inducible vascular smooth muscle-specific PPARγ deficient mice, which seems to involve oxidative stress due to decreased expression of SOD3 (169). Interestingly, it was also shown that endothelial-specific expression of dominant negative PPARγ (V290M) exhibited endothelial dysfunction and an augmented pressor response to AngII (170). The enhancement of AngII-induced endothelial dysfunction in this mouse is associated with enhanced oxidative stress and decline in antioxidant genes (catalase and SOD3) in carotid arteries (171). The above findings illustrate the complex relations among the AT1 receptor, HIF-1α and PPARγ in mediating hypertension, vascular remodeling and endothelial dysfunction.

9. Conclusions and future directions

An overview of AT1 receptor signaling and recent findings in cardiovascular physiology are summarized in this review. AT1 receptor signal transduction pathways are a central cascade in RAAS, and emerging evidence reveals the complexity of AT1 receptor signaling, including crosstalk with other signaling cascades in addition to direct interaction with other receptors and proteins. AT1 receptor facilitates various intracellular signaling pathways thus contributing to vascular remodeling, endothelial dysfunction, cardiovascular diseases, atherosclerosis and end organ damage. Therefore, elucidating the complete picture of AT1 signaling is beneficial to control hypertension and cardiovascular diseases. Genomic and proteomic approaches in coordinance with system biology will help further understand the mechanism by which AT1 receptor mediates cardiovascular dysfunctions. In addition, since most of the findings reviewed here are based on cell/animal models, the need to expand research in human samples and translational research will be important to control cardiovascular diseases in humans.

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Abbreviations

AAA	abdominal aortic aneurysm
ADAM17	a disintegrin and metalloproteinase 17

ANO1	anoctamin-1
ARAP1	type 1 angiotensin II receptor-associated protein
ATRAP	AT1 receptor associated protein
AngII	angiotensin II
AT1 receptor	angiotensin II type 1 receptor
AT2 receptor	angiotensin II type 2 receptor
β-COP	Coatomer subunit β
BMX	bone marrow kinase
CHKA	choline kinase alpha
COPI	Coat Protein I
Drp1	dynamin-related protein 1
EC	endothelial cells
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
eIF4E	eukaryotic translation initiation factor 4E
eNOS	endothelial nitric oxide synthase
ER	endoplasmic reticulum
ERK	extracellular signal regulated kinase
GABA	Gamma-aminobutyric acid
GABARAP	Gamma-aminobutyric acid receptor-associated protein
GEF	Guanine nucleotide exchange factor
GLP	GEF-like protein
GPCR	G protein-coupled receptor
GRK	G protein-coupled receptor kinase
HB-EGF	Heparin-binding EGF-like growth factor
HIF-1α	hypoxia-inducible factor 1 alpha
IGF-1R	insulin-like growth factor-1 receptor
JAK2	Janus kinase 2
JNK	c-Jun N terminal kinase

LATS	large tumor suppressor kinase
MAPK	mitogen-activated protein kinase
MEK	MAPK/ERK kinase
MCP-1	monocyte chemoattractant protein-1
MFN2	Mitofusion 2
MLCK	myosin light chain kinase
MLCP	myosin light chain phosphatase
mTOR	mechanistic target of rapamycin
NADPH	nicotinamide adenine dinucleotide phosphate
NF-kB	nuclear factor kappa B
NFAT	Nuclear factor of activated T-cells
NKCC1	Na-K-Cl cotransporter isoform 1
NLRP3	NLR family pyrin domain containing 3
NO	nitric oxide
oxLDL	oxidized low density lipoprotein
PAI-1	plasminogen activator inhibitor-1
PAK1	p21-activated kinase 1
PARP	poly (ADP-ribose) polymerase
PDGFR	platelet-derived growth factor receptor
PI3K	phosphatidylinositol 3-kinase
PKA	protein kinase A
PKB	protein kinase B
PKC	protein kinase C
PLC	phospholipase C
PPARγ	peroxisome proliferator-activated receptor gamma
RAAS	renin-angiotensin-aldosterone system
RANKL	receptor activator of nuclear factor-kappa B
RAP1b	Ras-related protein
ROCK	Rho-associated protein kinase

ROS	reactive oxygen species
SOD	superoxide dismutase
SPAK	Ste20/SPS1-related proline/alanine-rich kinase
TAA	thoracic aortic aneurysm
TCF/LEF	(T-cell factor/lymphoid enhancer factor)
TGFβ1	transforming growth factor beta 1
TRIO	triple functional domain (PTPRF interacting)
VSMC	vascular smooth muscle cells
WISP1	Wnt1 inducible signaling pathway protein 1
WNK	with-no-lysine
YAP	Yes-associated protein

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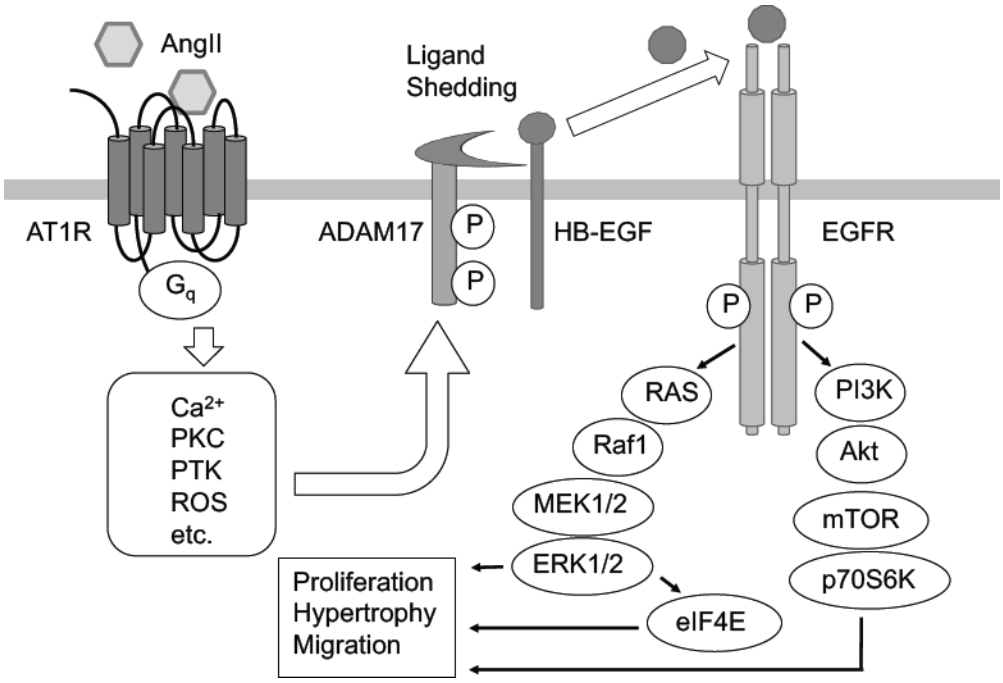

Figure 1. AT1 receptor signal transduction cascade through EGFR transactivation

AngII-activated AT1 receptor initiates classical second messenger-mediated signals such as Ca2+, elevation and PKC activation as well as PTK activation and ROS production via heterotrimeric G proteins, which then activate ADAM17 via phosphorylation. Activated ADAM17 causes shedding of EGFR ligands such as pro-HB-EGF, and activates EGFR. EGFR transactivation by AT1 receptor facilitates cellular hypertrophy, proliferation and migration via the Ras/Raf/MEK/ERK pathway and PI3K/Akt-PKB/mTOR pathway. EGFR: epidermal growth factor receptor; ADAM17: A Disintegrin And Metalloproteinase 17; MEK: MAPK/ERK kinase; mTOR: mamalian target of rapamycin; eIF4E: eukaryotic translation initiation factor 4E.

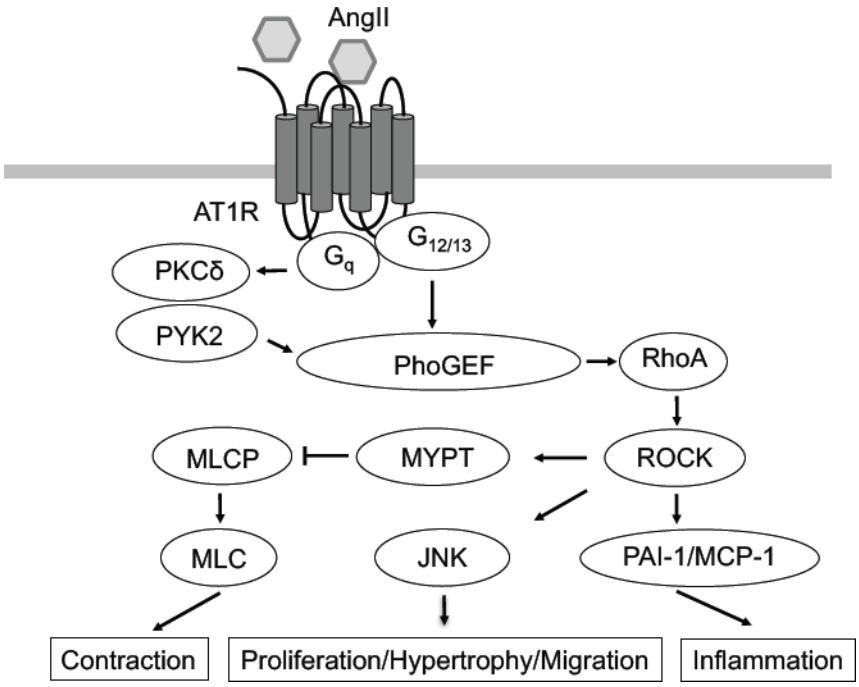

Figure 2. AT1 receptor signal transduction cascade through the Rho/ROCK pathway

The AT1 receptor interacts with heterotrimeric G proteins and activates Rho/ROCK pathway via RhoGEF. Through this pathway, AT1 receptor stimulates cellular contraction via MLC by inhibition of MLCP, cellular proliferation/hypertrophy via JNK, and inflammation via PAI-1/MCP-1. MLC: myosin light chain; MLCP: MLC phosphatase.

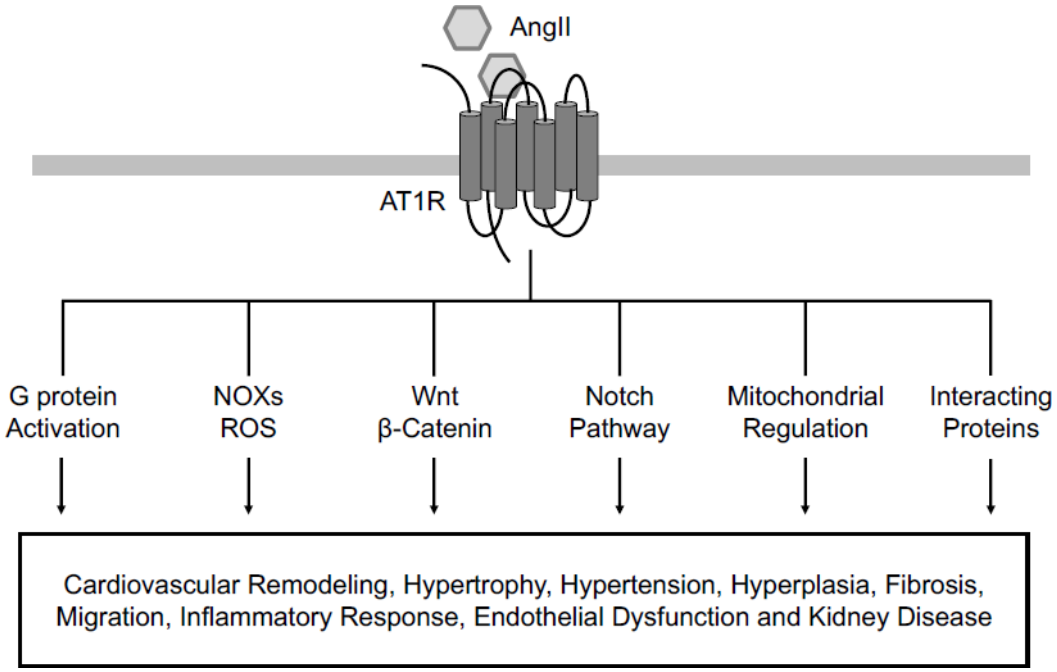

Figure 3. The new and complex mechanisms of AT1 receptor-mediated signaling in cardiovascular pathophysiology

Traditionally AT1 receptor is known to cause cardiovascular remodeling, hypertension and end organ damage via a few cascades including Gq/Ca^{2+}-PKC, ERK/MAPK and NOX/ROS. Although not all the functional significances have been identified, recent studies explored new signaling mechanisms by which the AT1 receptor may contribute to cardiovascular disorders, including Wnt, Notch, mitochondrial regulation and AT1 receptor interacting proteins. Elucidating the complexity of AT1 receptor signaling seems to be on the forefront of RAAS research to conquer cardiovascular disorders.

Table 1

Interactions between AT1 receptor and other proteins.

		General function	ATI related function	Ref
GPCRs	α_{1D} adrenergic receptor	growth/proliferation	promotes preeclampsia	(112)
	β_1 adrenergic receptor	increase cardiac output	enhance AT1 signaling	(110)
	β_2 adrenergic receptor	vasodilation	enhance AT1 signaling	(110)
	Bradykinin receptor B_2	vasodilation	enhance activation of Gq and Gi	(109)
	Dopamine receptor D_1	natriuresis, vasorelaxation	renal vascular resistance/sodium transport	(111)
	Prostaglandin F receptor	vasoconstriction	enhance vasoconstriction	(114)
	P2Y purinergic receptor 6	vasocontraction	mediate vascular remodeling	(113)
Other receptors	EGFR	growth/proliferation	mediate vascular remodeling	(116)
	OxLDL receptor	atherosclerosis formation	AT1 activation	(115)
Other proteins	ARAP1	unknown	AT1 trafficking to cell surface	(126)
	ATRAP	unknown	AT1 internalization and inhibition	(119)
	β-arrestin	receptor desensitization	biased agonism	(101)
	β-COP	intraGolgi transport	AT1 trafficking to cell surface	(132)
	Filamin A	anchoring membrane proteins	AT1 cytoskeleton coupling	(131)
	GABARAP	GABA(A) receptor trafficking	AT1 trafficking to cell surface	(129)
	GLP	unknown	stimulate hypertrophy	(128)
	Tublin	microtubule dynamics	AT1 trafficking to cell surface	(130)

AT1 receptor binds to various intracellular proteins through its C-terminal domain and facilitates diverse signaling.