Pleiotropic Effects of Angiotensin II Receptor Signaling in Cardiovascular Homeostasis and Aging

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Summary

Most of the pathophysiological actions of angiotensin II (Ang II) are mediated through the Ang II type 1 (AT1) receptor, a member of the seven-transmembrane G protein-coupled receptor family. Essentially, AT1 receptor signaling is beneficial for organismal survival and procreation, because it is crucial for normal organ development, and blood pressure and electrolyte homeostasis. On the other hand, AT1 receptor signaling has detrimental effects, such as promoting various aging-related diseases that include cardiovascular diseases, diabetes, chronic kidney disease, dementia, osteoporosis, and cancer. Pharmacological or genetic blockade of AT1 receptor signaling in rodents has been shown to prevent the progression of aging-related phenotypes and promote longevity. In this way, AT1 receptor signaling exerts antagonistic and pleiotropic effects according to the ages and pathophysiological conditions. Here we review the pleiotropic effects of AT1 receptor signaling in cardiovascular homeostasis and aging. (Int Heart J 2015; 56: 000-000)

Key words: Blood pressure, Cardiac remodeling, Development, G protein-coupled receptor, Reactive oxygen species

The renin-angiotensin system (RAS) plays a central role in the regulation of cardiovascular pathophysiology.

The classical pathway of RAS involves the conversion of angiotensinogen to angiotensin II (Ang II) via a two-step process facilitated by renin and angiotensin converting enzyme (ACE). Ang II is the pivotal bioactive molecule of RAS, and induces vasoconstriction, sodium and water retention, and activation of the sympathetic nervous system. On the other hand, RAS also has deleterious effects on the heart and vessels as a form of cardiovascular remodeling, especially through local activation of RAS in tissues.1,2

Most of the pathophysiological actions of Ang II in the cardiovascular system are mediated through Ang II type 1 (AT1) receptors.3 The AT1 receptor is a typical member of the G protein-coupled receptor family, the structure of which is characterized by 7 transmembrane-spanning a-helices.4 While a single form of AT1 receptor exists in humans, mice possess two isoforms (AT1a and AT1b), which are the products of individual genes (Agtr1a and Agtr1b). The AT1a receptor is the major isoform of mouse AT1 receptor, and the Agtr1a gene that encodes the AT1a receptor is a mouse homolog to the single human AGTR1 gene that encodes the human AT1 receptor. AT1 receptors are activated upon binding to Ang II, but recent studies have demonstrated they are also activated by mechanical stress in the absence of Ang II through conformational switch of the receptor.5-7 AT1 receptor blockers (ARBs) are non-peptide compounds that selectively bind to AT1 receptors and inhibit Ang II-induced receptor activation.8 ARBs have a common chemical structure consisting of biphenyl-tetrazol and imidazole groups, but possess the drug-specific property of inverse agonist activity that can inhibit Ang II-independent constitutive activity and mechanical stress-induced receptor activation.9-11 Several ARBs are clinically available as a highly effective and well-tolerated class of drugs for the management of hypertension. In addition, clinical trials have demonstrated that ARBs provide cardiovascular protection and reduce death and hospitalization in patients with heart failure.12,13 Furthermore, it has been reported that inhibition of AT1 receptor-mediated signals in rodents delays the progression of aging-related phenotypes and promotes longevity,14-16 suggesting that AT1 receptor signaling is involved in the aging process per se. This review focuses on the pleiotropic effects of AT1 receptors in the cardiovascular system and the roles of AT1 receptor signaling in the aging process.

Physiological Roles of AT1 Receptors for Blood Pressure and Electrolyte Homeostasis and Organ Development

Low intake of salt or loss of fluid leads to a reduction in extracellular volume and stimulates secretion of renin. Ang II is produced as a consequence of sequential processing by renin and ACE, and exerts diverse systemic effects through AT1 receptors, such as systemic vasoconstriction, sodium and water...
retention, thirst response, and activation of sympathetic nervous system. All of these actions in combination reverse hypovolemia or hypotension. Thus, the AT1 receptor is required for homeostatic regulation of blood pressure and electrolyte and water balance.

Mice with targeted disruption of both genes encoding AT1 receptors (Agtr1a and Agtr1b) showed developmental abnormalities in kidney characterized by tubular atrophy with interstitial expansion, papillary atrophy, and manifested severe impairment of concentrating urine. Similar abnormalities of renal structure and function were also caused by treatment of newborn rats with ARB during the neonatal period. These results clearly indicate that the AT1 receptor is essential for normal development and function of the kidney. In addition, the use of ACE inhibitors or ARBs in pregnant women increases the risk of fetal disorders, such as oligohydramnios, prolonged hypotension, renal failure, or bone malformations. Therefore, administration of ACE inhibitors or ARBs is contraindicated in pregnant or breast-feeding women. Taken together, the AT1 receptor plays an essential role in the regulation of cardiovascular homeostasis and organ development in both humans and rodents.

**AT1 Receptor Signaling in Cardiac Remodeling and Heart Failure**

In pathological conditions such as hypertension, myocardial infarction, cardiomyopathy, or valvular heart diseases, hemodynamic overload induces hypertrophic growth of cardiomyocytes. Pathological growth of cardiomyocytes alters the collagen network surrounding the myocardium and promotes interstitial fibrosis. Although cardiac hypertrophy is initially compensatory and beneficial, the prolongation and excess of this process lead to deleterious outcomes such as congestive heart failure, arrhythmia, and sudden death. In a study cohort of never-treated hypertensive patients, higher concentrations of plasma Ang II were closely associated with greater left ventricular mass. Subsequent studies revealed that insufficient suppression of Ang II after high salt intake or hyper-responsiveness to Ang II was associated with higher left ventricular mass in hypertensive patients independently of blood pressure levels. In rats, Ang II infusion induced cardiac hypertrophy via activation of the AT1 receptor independently of blood pressure elevation, and cardiac-specific overexpression of the AT1 receptor in mice also induced cardiac hypertrophy, interstitial fibrosis, and contractile dysfunction. These results suggest that activation of the AT1 receptor is sufficient for inducing cardiac remodeling independently of blood pressure elevation.

The blockade of AT1 receptor signaling is effective at preventing the progression of heart failure in a variety of animal models. At 4 weeks after myocardial infarction, AT1a receptor-deficient mice showed a better survival rate with significant improvement of left ventricular dilation, systolic dysfunction, and cardiac fibrosis, as compared with control mice. In a model of doxorubicin-induced cardiomyopathy, AT1a receptor-deficient mice showed less severe cardiac dysfunction with a decrease in cardiomyocyte apoptosis, as compared with control mice. Muscle LIM protein (MLP) is involved in organization of cellular architecture and function as a mechanical stretch sensor. MLP-deficient mice showed marked cardiac dilatation with contractile dysfunction, but genetic disruption of the AT1a receptor attenuated the cardiomyopathic phenotypes in MLP-deficient mice. According to a meta-analysis that evaluated the effects of antihypertensive therapy on cardiac hypertrophy, ARBs were the most effective class of drugs for reducing left ventricular mass in patients with essential hypertension. Clinical trials have also demonstrated that ARBs reduce death and hospitalization in the broad spectrum of patients with heart failure.

A large number of experiments have demonstrated that activation of the AT1 receptor stimulates diverse intracellular signaling pathways in both a Gq, protein-dependent and -independent manners. AT1 receptor activation enhances production of reactive oxygen species (ROS) via NAD(P)H oxidase, and enhances production of extracellular matrix proteins in cardiac fibroblasts. AT1 receptor activation stimulates mitogen-activated protein kinase (MAPK) family members such as extracellular signal-regulated protein kinases (ERKs), c-Jun N-terminal kinase, and p38 MAPK. Activated ERKs enhance protein synthesis via activation of p70 S6 kinase and ribosomal RNA transcription. ERKs also phosphorylate and activate several transcription factors such as GATA4 or transcriptional coactivators such as p300 and CBP, and thereby up-regulate the gene expression related to hypertrophic responses. AT1 receptor activation also stimulates G protein-independent signaling pathways such as activation of the JAK-STAT pathway or β-arrestin-mediated activation of ERKs.

**Deleterious Effects of AT1 Receptor Signaling Throughout the ‘Cardiovascular Continuum’**

AT1 receptor signaling plays a major role in the pathogenesis of other cardiovascular disorders, such as hypertension or atherosclerotic vascular disease. Hypertension is a pathological condition characterized by self-acceleration, in which excessive and persistent activation of RAS induces vasoconstriction and promotes vascular hypertrophy through direct and indirect hemodynamic effects. Arteriolar hypertrophy and endothelial dysfunction give rise to the elevation of blood pressure and contribute to the transition from prehypertension to established hypertension. It has been reported that treatment of hypertensive patients with an ARB significantly reduced the incident risk of hypertension, indicating that AT1 receptor signaling is profoundly involved in the pathogenesis of hypertension.

The mechanisms underlying the progression of atherosclerosis include vascular inflammation, generation of ROS, and endothelial dysfunction. Experimental evidence has indicated that AT1 receptor activation is profoundly involved in all of these pathways. For example, AT1 receptor activation enhances the transcriptional activity of nuclear factor-kappa B, which serves as a unifying signaling molecule for inflammation. It also stimulates the release of proinflammatory cytokines such as interleukin (IL)-6 and promotes the recruitment of macrophages and T cells through generation of adhesion molecules and chemokines. Local generation of ROS impairs endothelial function, induces tissue inflammation, and promotes vascular remodeling. Furthermore, activation of the AT1 receptor induces vasoconstriction, alters the composition of the extracellular matrix, and enhances migration and proliferation of vascular smooth muscle cells. By evoking these multiple cellular...
.responses, AT₁ receptor signaling contributes to the progression of atherosclerosis.

AT₁ receptor signaling is also involved in the pathogenesis of insulin resistance, which is a hallmark of metabolic syndrome and type 2 diabetes mellitus. Recent clinical trials have suggested that pharmacological blockade of the AT₁ receptor improves insulin sensitivity and reduces the incidence of diabetes in patients at high risk. The interactions between Ang II- and insulin-mediated signaling pathways are complex. For example, activation of the AT₁ receptor inhibits the metabolic actions of insulin via the phosphoinositide 3-kinase pathway, but synergistically promotes its proliferative effects via the MAPK pathway. Conversely, both hyperglycemia and hyperinsulinemia activate AT₁ receptor signaling, which may contribute to the development of hypertension in patients with insulin resistance. It has been reported that acute infusion of Ang II in rats inhibited the early phase of insulin secretion, and that treatment with ARB stimulated the early phase of insulin secretion in mice which underwent ovariectomy. In Zucker diabetic fatty rats, RAS inhibition improved islet architecture and attenuated islet fibrosis. These results suggest that local activation of the AT₁ receptor impairs the structure and function of β cells.

Therefore, AT₁ receptor activation not only elevates blood pressure, but also initiates vascular dysfunction and cardiac hypertrophy, and increases the risk of myocardial infarction. AT₁ receptor activation further promotes cardiac remodeling, and finally results in congestive heart failure with high morbidity and mortality. It is now widely recognized that the AT₁ receptor is profoundly involved in virtually all stages of the "Cardiovascular Continuum".

Deleterious Effects of AT₁ Receptor Signaling on Aging-Related Disorders

Aging is defined as a progressive loss of function with advancing age, which increases the risks of aging-related disorders. It has been demonstrated that AT₁ receptor signaling is involved in the pathophysiological processes of various aging-related diseases, including not only cardiovascular diseases and heart failure, but also chronic kidney disease, dementia, osteoporosis, and cancer.

For example, AT₁ receptor signaling contributes to the progression of chronic kidney disease. Ang II exerts its vasoconstrictor effect predominantly on the post-glomerular arterioles, thereby increasing glomerular hydrostatic pressure and inducing ultrafiltration of plasma proteins, which may initiate and promote chronic renal damage. Besides exerting hemodynamic effects, Ang II also directly accelerates renal damage by non-hemodynamic effects, which include an increase in ROS production, upregulation of cytokines and cell adhesion molecules, an increase in synthesis of extracellular matrix proteins, and activation and recruitment of macrophages. ARBs reduce proteinuria and decline of the glomerular filtration rate in patients with chronic kidney disease, and thereby provide renal protection.

Accumulating evidence from basic research has also indicated the possible involvement of the central RAS in ischemic brain damage or neuropathology of Alzheimer’s disease. It has been reported that ARB at a subpressor dose suppressed ROS production and decline in cerebral blood flow, and thereby reduced the ischemic areas of the brain after cerebral artery occlusion in mice. Treatment with an ARB also reduced the accumulation of β-amyloid proteins in the brain and attenuated the development of cognitive deterioration in a mouse model of Alzheimer’s disease, suggesting that AT₁ receptor signaling may contribute to the pathological process of Alzheimer’s disease.

Recent basic and clinical studies have indicated that the RAS may also be involved in bone metabolism. Antihypertensive treatment with ACE inhibitors had beneficial effects on bone metabolism and reduced the risk of bone fractures. Administration of Ang II to ovariectomized rats accelerated osteoporosis, accompanied by an increase in osteoclast activity, and the treatment of hypertensive rats undergoing ovariec-tomy with ARB attenuated a decrease in bone density and an increase in osteoclast activity. Thus, AT₁ receptor activation may accelerate osteoporosis by activating osteoclasts.

Furthermore, AT₁ receptor signaling is involved in the process of carcinogenesis. AT₁ receptors are expressed in several human cancer cell lines such as pancreatic cancer cell lines and prostate cancer cell lines, and the growth of cancer cells was suppressed by treatment with ARBs. Additionally, in a subpopulation of ER-positive, ERBB2-negative breast cancer cases, the gene encoding the AT₁ receptor (AGTR1) was highly overexpressed. Stimulation with Ang II induced transformation of AGTR1-overexpressing mammary epithelial cells into a highly invasive phenotype, and ARB treatment reduced tumor growth in AGTR1-positive breast cancer xenografts. The growth of tumor cells engrafted in AT₁ deficient mice was reduced, as compared with that in wild-type mice, accompanied by reduction in tumor-related angiogenesis. In a mouse model of lung adenocarcinoma, Ang II induced proliferation of myeloid progenitor cells in spleen via activation of AT₁a receptors, thereby increasing the supply of tumor-associated macrophages to promote cancer development. These findings indicate that AT₁ receptor signaling plays an important role in tumor growth and progression through enhancing tumor cell proliferation, tumor-associated angiogenesis, and tumor-associated macrophage production.

In high-risk animals with hypertension, inhibition of RAS leads to better survival and promotes longevity. Treatment of 1-month-old stroke-prone spontaneously hypertensive rats (SHR-SP) with an ACE inhibitor or ARB doubled the life span to 30 months, which was comparable to that of normotensive Wistar-Kyoto rats. The effect of life span extension was associated with preservation of cardiac function as well as endothelial function by the treatment with an ACE inhibitor or ARB.

AT₁ Receptor Signaling in Physiological Aging

It has been reported that inhibition of RAS prolongs the physiological process of aging in rodents. Administration of an ACE inhibitor or ARB to normal CF1 mice or Wistar rats prolonged their life span, which was accompanied by a decrease in myocardial and renal fibrosis. In the hearts of aging mice, administration of an ACE inhibitor induced a decrease in apoptosis and suppression of a decrease in mitochondrial number and mitochondrial expression of superoxide dismutase. Furthermore, genetic disruption of the AT₁ receptor not only prevented aging-related progression of cardiac...
hypothesis, and pathological aging-related diseases later in life.

AT$_1$ Receptor Signaling from the Viewpoint of Evolutionary Theories of Aging

Progressive loss of function in multiple organs with aging is clearly deleterious for survival and procreation of individual organisms, and this raises the long-standing question of why and how evolution of aging has occurred in multicellular organisms. In the wild and unprotected environments, natural mortality is mostly caused in the young population by extrinsic hazards, such as infection, predation, starvation, or cold. Under such conditions, only a few individuals live for a long enough period to be aged. According to the mutation-accumulation theory, the force of natural selection is progressively weakened with increasing age, which permits accumulation of deleterious mutations exerting their effects only late in life. According to the antagonistic pleiotropy theory, pleiotropic genes that increase survival and procreation early in life are favored and accumulated over the generations by natural selection, even if these genes are deleterious late in life. This theory is relevant to the idea of a “trade-off” between early-life fitness and late-life fitness.

As mentioned above, activation of the AT$_1$ receptor is profoundly involved in the progression of various aging-related diseases. On the other hand, the AT$_1$ receptor is necessary for normal development of the kidney during the embryogenic and neonatal periods. In addition, activation of the AT$_1$ receptor induces systemic vasoconstriction, and sodium and water retention, which are essential for hemodynamic homeostasis and apparently beneficial for survival. Therefore, the AT$_1$ receptor represents typical antagonistic pleiotropy, because it provides beneficial and adaptive effects early in life, but in contrast, deleterious effects promoting cardiovascular and multi-organ damage later in life.

Conclusion: AT$_1$ receptor signaling has pleiotropic effects. These effects are beneficial in early life, whereas in later life they are deleterious, leading to the progression of various aging-related diseases. Thus, the AT$_1$ receptor has the functions of ‘antagonistic pleiotropy’ in the physiological process of growth and aging (Figure). Further investigations of the antagonistic pleiotropic effects of the AT$_1$ receptor will provide insights into the mechanisms responsible for physiological aging and pathological aging-related diseases and hopefully will lead to the development of novel therapeutics.

Disclosures


References


