Chapter

The Renin-Angiotensin-Aldosterone System: Mechanisms, Pathophysiological Impacts, and Emerging Therapeutic Strategies

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Abstract

The renin-angiotensin-aldosterone system (RAAS) is a pivotal hormonal mechanism integral to cardiovascular and renal homeostasis. This comprehensive review delineates the intricate pathways of RAAS, highlighting its classical and newer axes and their multifaceted roles in physiological and pathological states. We explore the foundational research that has expanded our understanding of RAAS beyond its traditional scope, emphasizing the critical balance between the ACE/Ang II/AT1 axis and the protective ACE2/Ang 1–7/Mas axis. The manuscript delves into RAAS's impact on various organ systems, particularly the cardiovascular and renal, and underscores the system's significance in hypertension, diabetes, and kidney diseases. The review also scrutinizes the therapeutic interventions targeting RAAS, including pharmacological advancements and potential novel approaches. Furthermore, it outlines the challenges and future directions in RAAS-related research, such as personalized medicine, combination therapies, and the development of agonists for the Mas receptor. The evolving landscape of RAAS modulation offers promising avenues for managing complex diseases and emphasizes the need for continued investigation to harness its full therapeutic potential.

Keywords: renin-angiotensin-aldosterone system, angiotensin II, angiotensin-converting enzyme 2, mas receptor, RAAS inhibition, hypertension, cardiovascular protection, diabetic nephropathy, therapeutic targets

1. Introduction

The renin-angiotensin-aldosterone system (RAAS) is a pivotal hormonal system in the human body. Discovered over a century ago, renin was first identified in 1836 when Richard Bright noted the correlation between cardiovascular and renal diseases in his writings, stating, "Cardiac hypertrophy seems to keep pace, to some extent, with the progress of renal disease" [1]. In 1898, Tigerstedt and Bergmann

isolated the enzyme renin from the kidneys. Skeggs and colleagues were the first to obtain pure angiotensin. Building on the knowledge provided by these researchers, the study of the role of the renin-angiotensin-aldosterone system in normal and pathological states began, leading to the definition of the classical RAAS pathway in 1961. However, research in this field continues, and studies in the 1990s have proven that the main effector of the RAAS is angiotensin II, which is derived from the progressive proteolysis of angiotensinogen. In addition, angiotensin and aldosterone are also upstream regulatory factors [2]. Over the past few decades, we have seen a considerable expansion of the RAAS. Although it involves multiple organ functions, its primary function seems to have remained largely unchanged. The systemic RAAS cascade begins with angiotensinogen (AGT) produced by the liver, which is converted to angiotensin I (ANG I) by renin secreted by the juxtaglomerular cells of the kidney. Angiotensin-converting enzyme (ACE) secreted by the lungs and kidneys then transforms ANG I into ANG II, while angiotensin-converting enzyme 2 (ACE2) further breaks down ANG II into ANG 1–7 [3].

The primary function of RAAS in altering arterial blood pressure is to regulate peripheral vascular resistance. Angiotensin II exerts its effects through two receptor subtypes, AT1R and AT2R. AT1R mediates the classic actions of ANG II, with AT1 receptors activating neurons in the paraventricular nucleus (PVN), supraoptic nucleus (SON), and medial preoptic area (MnPO) of the hypothalamus, increasing the release of antidiuretic hormone and directly inducing thirst, thereby regulating fluid balance and thirst sensation [4]. Additionally, in terms of excretion, angiotensin, synthesized by Bumpus, Schwarz, and Page in 1957, triggered an in-depth study of the chemistry of angiotensin. Angiotensin II regulates the metabolism of water and sodium by the kidney through direct and indirect effects [5]. Its direct effects include changes in glomerular filtration rate (GFR) and regulation of sodium reabsorption in the renal tubules. By constricting the efferent arterioles, Ang II helps maintain the relative stability of GFR under conditions of hypotension. However, long-term high concentrations of Ang II induce the expression of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), through the activation of signaling pathways like nuclear factor-kappa B (NF-κB). These inflammatory factors can lead to renal tubulointerstitial fibrosis and a decline in renal function, resulting in glomerulosclerosis and a decrease in function [6]. The regulation of sodium reabsorption is achieved by stimulating the sodium-hydrogen exchanger and the sodium-phosphate cotransporter. Ang II stimulates the adrenal cortex to secrete aldosterone, which increases the reabsorption of Na + and the secretion of K+ by promoting the exchange of Na + -K+ in the distal tubules and collecting ducts. Thus, the body maintains a dynamic balance of Na + and K+ concentrations. Vascular resistance is the second factor affecting arterial blood pressure, and angiotensin II itself is one of the most potent vasoconstrictors, activating a series of signaling pathways, including phospholipase C (PLC) and protein kinase C (PKC), leading to an increase in intracellular calcium ion concentration in vascular smooth muscle cells (VSMCs) and activating NADPH oxidase to increase the production of reactive oxygen species (ROS) [7]. ROS promote smooth muscle cell contraction and cause endothelial dysfunction; Ang II can also induce the expression of pro-inflammatory cytokines such as TNF-α, IL-6, monocyte chemoattractant protein 1 (MCP-1), interleukin-1β (IL-1β), and intercellular adhesion molecule 1 (ICAM-1) through the activation of inflammatory signaling pathways, such as the NF-κB pathway [8]. These inflammatory factors can promote the migration of inflammatory cells, exacerbate inflammatory responses, and the proliferation of vascular wall cells; induce the synthesis and

secretion of extracellular matrix collagen and fibronectin by vascular smooth muscle cells and fibroblasts, leading to thickening and hardening of the vascular wall, thus causing vasoconstriction.

Angiotensin II (Ang II) exerts various biological effects through its binding to the angiotensin II type 2 receptor (AT2R). Contrary to the proliferative and pro-inflammatory responses mediated by the classic AT1R, the activation of AT2R is generally considered to have a protective effect. The activation of AT2R can cause the relaxation of vascular smooth muscle cells, leading to vasodilation and a reduction in blood pressure. This contrasts with the vasoconstrictive effect mediated by AT1R, inhibiting the production of various pro-inflammatory cytokines, such as TNF-α and IL-6, thereby reducing inflammatory responses; it can inhibit fibrotic reactions, reducing tissue damage and functional loss; it has neuroprotective effects in the nervous system, including reducing neuroinflammation and promoting neurogenesis; in some cases, it has an anti-nociceptive effect, reducing chronic pain by inhibiting neuroinflammation and reducing oxidative stress [8]. The activation of AT2R is generally considered beneficial, and capable of counteracting the harmful effects of Ang II induced by AT1R. These protective effects make AT2R a potential target for the treatment of cardiovascular diseases, kidney diseases, and neurological disorders [9].

The RASS system mainly has two types. One is the ACE/Ang II/AT1 axis, and the other is the ACE2/Ang1–7/Mas axis. They have a significant impact on the cardiovascular system and other physiological systems. This axis consists of angiotensin-converting enzyme 2 (ACE2), angiotensin-(1–7) [Ang-(1–7)], and the Mas receptor (MasR) [9]. Ten years ago, Donoghue et al. [10] discovered ACE's homologous compound ACE2 in the ventricles of patients with heart failure, which has 42% homology in the sequence of the active site with ACE. ACE2 is a zinc-dependent metalloproteinase containing 805 amino acids and is a type 1 transmembrane protein (N-terminus outside the cell, C-terminus inside the cell). It is mainly expressed in vascular endothelial cells and is highly limited to 23 types of tissues, such as the heart, kidney, and intestine [11]. In brain tissue, it can act as a central regulator of cardiovascular function and is mainly distributed in vascular endothelial cells, type I and type II alveolar epithelial cells, pulmonary vascular smooth muscle cells, and bronchial epithelial cells in the lung [12]. ACE2 is also a single carboxypeptidase, removing a single amino acid from the carboxyl terminus of the substrate. Its main substrate is Ang II, and ACE2 can efficiently catalyze the transformation of Ang II into Ang1–7, which is about 400 times more active than hydrolyzing Ang I [13]. When the concentration of Ang I is high, ACE2 can also convert Ang I into Ang1–9, which can be further degraded into Ang1–7 by ACE or other enzymes [14]. Other hydrolysis substrates include Apelin-13, Apelin 36, Neurotensin 1–8, Dynorphin A(1–13), [des-Arg9]-Bradykinin, and [Lys-des-Arg9]-Bradykinin. Ang1–7 is a vasodilatory peptide that, through the Mas receptor, can promote the activation of endothelial nitric oxide synthase (eNOS), increase the concentration of nitric oxide (NO), improve endothelial cell function, reduce pulmonary inflammation, and protect the heart and lungs. This axis is generally considered an antagonistic mechanism of the classical RAS system because of its anti-inflammatory, anti-fibrotic, and anti-proliferative protective effects. ACE2 reduces the level of Ang II by converting Ang II into Ang-(1–7), thus playing a protective role. The Mas receptor is a G protein-coupled receptor that mainly mediates the biological effects of Ang-1-7, causing vasodilation, anti-inflammatory, and antiproliferative effects through the activation of signaling pathways. In recent years, more and more studies have shown that the mutual regulation of the two sub-axes is like the concept of "complementarity of yin and yang, mutual assistance" in Tai Chi (**Figure 1**).

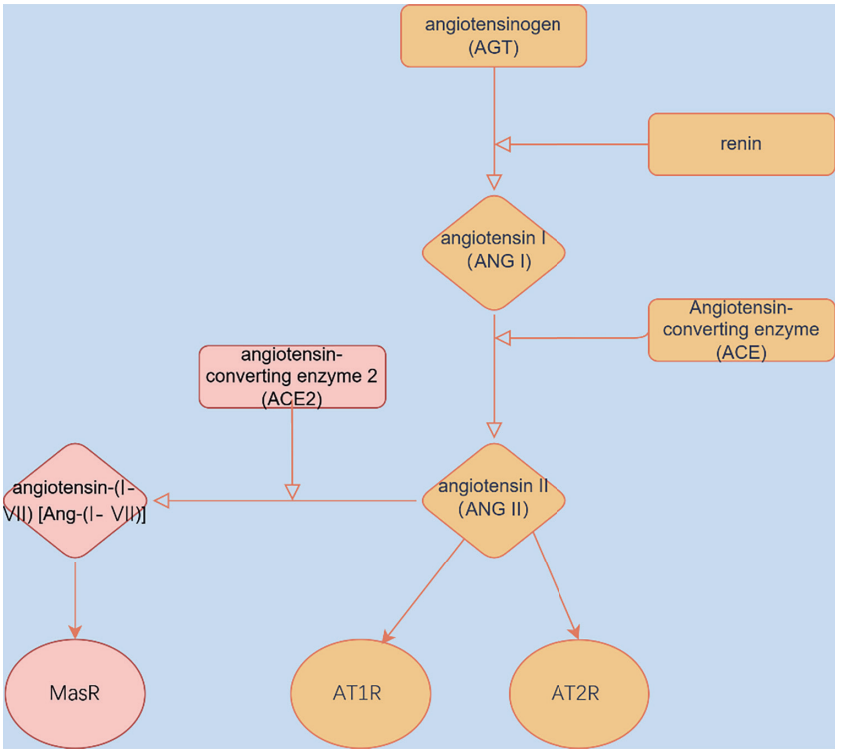

Figure 1.
The Renin-Angiotensin System (RAS) Pathway.

2. The renin-angiotensin-aldosterone system (RAAS) exerts a profound influence on multiple physiological systems, affecting their regulation and balance

This section delves into the multifaceted impacts of RAAS, particularly focusing on its role in the respiratory, circulatory, endocrine, and renal systems.

2.1 Respiratory system

Pulmonary arterial hypertension (PAH) is a critical cause of right heart failure. During the disease process, excessive proliferation and remodeling of pulmonary arterial smooth muscle cells, endothelial dysfunction, imbalance of vasoactive substances, accumulation of perivascular inflammatory cells, and intraluminal thrombosis lead to a gradual increase in pulmonary arterial pressure, inducing right heart failure and functional decline [12, 13, 15]. Damage to pulmonary vascular endothelial cells is considered the initiating link and a necessary condition for pulmonary vascular remodeling [16]. The renin-angiotensin system (RAAS) plays a crucial role in endothelial dysfunction and vascular remodeling. Ang II, through the AT1 receptor, mediates a series of inflammatory reactions, inducing the release of inflammatory cytokines such as IL-6 and TNF-α from vascular endothelial cells and smooth muscle cells. Studies have shown that Ang II also promotes the expression of cell adhesion molecules and chemokines through the activation of the nuclear factor-kappa B (NF-κB) signaling pathway, thereby facilitating the aggregation of inflammatory cells and

vascular remodeling [17]. Ang II can also activate the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway and transforming growth factor-beta (TGF-β) pathway through oxidative stress and vascular smooth muscle cell proliferation, further promoting myocardial cell hypertrophy and interstitial fibrosis, leading to right ventricular remodeling [18].

In contrast, the ACE2/Ang1–7/Mas axis has a protective role in pulmonary arterial hypertension (PAH). Ang1–7, mediated by the Mas receptor, exerts anti-inflammatory and antiproliferative effects, inhibiting the proliferation and migration of vascular smooth muscle cells, thereby alleviating vascular remodeling. Studies indicate that Ang1–7 can downregulate the expression of inflammatory cytokines (such as IL-6 and TNF-α), suppress the activation of the NF-κB signaling pathway, and reduce inflammatory responses [19]. Additionally, Ang1–7 can alleviate the pathological process of PAH through antioxidant stress and improvement of endothelial function. Other studies have shown that ACE2-transfected human adipose-derived mesenchymal stem cells (ACE2-hAMSCs) significantly enhance migration and angiogenesis capabilities [20]. In a rat model of monocrotaline-induced pulmonary arterial hypertension, transplantation of ACE2-overexpressing hAMSCs resulted in overexpression of ACE2 in lung tissue and downregulation of Ang II expression [9]. ACE2 enhanced the paracrine effects of hAMSCs and promoted blood vessel growth. The expression of factors such as VEGF-a, bFGF, Ang-1, and TGF-β reduced inflammatory factors. At the same time, other studies have shown that Ang1–7 can inhibit myocardial cell hypertrophy and fibrosis through the activation of the Cyclic AMP/Protein Kinase A (cAMP/PKA) signaling pathway [21].

Furthermore, Ang1–7 can alleviate pathological changes by improving myocardial blood flow and oxygen supply. These studies suggest that enhancing the activity of the ACE2/Ang-(1–7)/Mas axis may provide new ideas for the treatment of PAH and right ventricular hypertrophy (RVH). However, further clinical studies are still needed to verify the safety and efficacy of these therapies in humans.

2.2 Circulatory system

2.2.1 Hypertension and heart failure

Hypertension is a common cardiovascular disease caused by the abnormal activation of the RAAS. In hypertension, Ang II activates multiple signaling pathways through the AT1 receptor on myocardial cells, including the extracellular signal-regulated kinases (ERK1/2), Janus kinase/signal transducer and activator of transcription (JAK/STAT), and phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT) pathways. The activation of these pathways leads to myocardial cell hypertrophy, an increase in cell volume. Ang II can also promote the activation and proliferation of fibroblasts, increasing the deposition of extracellular matrix (ECM), such as collagen, leading to cardiac fibrosis and increased stiffness [22]. These changes can lead to a decrease in cardiac compliance and further promote the progression of myocardial hypertrophy. Ang II regulates the contractility of myocardial cells by affecting intracellular calcium ion concentrations. Abnormal calcium regulation can lead to functional changes in myocardial cells and promote hypertrophy, exacerbating myocardial remodeling [23]. AT1R induces the upregulation of TGF-β through oxidative modification of proteins, lipids, and DNA, destroying cell structures and causing cell death. In particular, NOX2 and NOX4 are highly expressed in myocardial cells and exacerbate myocardial hypertrophy and fibrosis

by activating the MAPK and NF-κB signaling pathways, ultimately leading to left ventricular hypertrophy [9].

Studies have shown that ACE inhibitors and Ang II receptor blockers can significantly reduce the levels of inflammatory markers in patients with hypertension, thereby reducing vascular inflammation and remodeling [24]. However, in recent years, a new type of drug, angiotensin receptor-neprilysin inhibitors (ARNIs), has been developed to exert multiple effects by combining angiotensin II receptor blockers (ARBs) and neprilysin inhibitors [25]. The representative drug Sacubitril/Valsartan has shown superior efficacy in the treatment of cardiovascular diseases such as heart failure and left ventricular hypertrophy [26]. In addition to the Valsartan part acting as an ARB, selectively blocking the binding of Angiotensin II to its AT1 receptor, the Sacubitril part also inhibits neprilysin, preventing the degradation of various beneficial peptides (such as natriuretic peptides, vasodilatory peptides, and endorphins) [27]. These peptides help improve heart function through vasodilation, diuresis, reduction of cardiac load, and anti-fibrotic effects. At the same time, these peptides also have antiproliferative and anti-fibrotic effects, preventing myocardial fibrosis and ventricular remodeling. Compared with traditional ARB drugs, the multi-mechanism action on the heart more effectively inhibits myocardial fibrosis, promotes the reversal of myocardial remodeling, and reduces the incidence of cardiac events [28]. Clinical studies, such as the Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitors (ARNI) with Angiotensin-Converting Enzyme Inhibitors (ACEI) to Determine Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, aimed to determine the prognostic performance of B-type natriuretic peptide (BNP) measurements before and during treatment with sacubitril/valsartan. The results of the trial indicated that ARNI significantly outperformed traditional angiotensin II receptor blockers (ARBs) in reducing heart failure hospitalization rates and cardiovascular mortality. In addition to ARNI, other new drugs, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors, have protective effects on the cardiovascular system, especially in hypertension and left ventricular hypertrophy, which has gradually been discovered and studied [29]. The therapeutic mechanism of SGLT2 inhibitors was initially to reduce the reabsorption of glucose in the proximal tubules of the kidney by inhibiting the function of the SGLT2 protein, thereby lowering blood glucose levels. However, in addition to its blood sugar-lowering effect, the protective effects of SGLT2 inhibitors in the cardiovascular system, especially in hypertension and left ventricular hypertrophy, have also been discovered and studied [28]. SGLT2 inhibitors reduce sodium reabsorption in the kidney and increase the excretion of urinary sodium and water retention, leading to a decrease in blood volume, thereby lowering blood pressure. After reducing blood volume and blood pressure, it can reduce the afterload of the left ventricle and alleviate the progression of left ventricular hypertrophy. SGLT2 inhibitors can also increase fatty acid oxidation and ketone body utilization under conditions of limited myocardial oxygen supply, reducing glucose dependence, and placing myocardial cells in a more favorable position in energy metabolism. SGLT2 inhibitors inhibit fibrosis-related signaling pathways (such as the TGF-β pathway) as well as reduce oxidative stress, thereby protecting myocardial structure and function [29]. In addition to these two types of drugs, there are non-steroidal selective mineralocorticoid receptor antagonists and new anti-fibrotic drugs that can reverse myocardial fibrosis and left ventricular hypertrophy [30].

The protective role of the ACE2/Ang1–7/Mas axis in hypertension has been widely studied. Ang1–7 can promote the release of nitric oxide (NO) by endothelial cells, which is a potent vasodilator. NO binds to soluble guanylate cyclase (sGC), activating

the enzyme. Activated sGC catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) [24]. cGMP activates protein kinase G (PKG), which further promotes calcium pump activity in the sarcoplasmic reticulum, reducing intracellular calcium concentration and causing smooth muscle relaxation [17, 18, 20]. cGMP can also reduce the sensitivity of smooth muscle cells to calcium through other signaling pathways, further promoting relaxation [26]. In addition, it can increase the production of prostacyclin, further promoting vasodilation and lowering blood pressure. Ang1–7 regulates kidney function through the Mas receptor, inhibiting sodium reabsorption in the renal tubules and promoting the excretion of sodium and water, thereby reducing body blood volume and lowering blood pressure. In the renal tubules, it inhibits the activity of sodium-hydrogen exchanger 3 (NHE3) and sodium-chloride cotransporter (NCC), which are important transport proteins responsible for sodium ion (Na+) reabsorption [22]. When their activity is inhibited, sodium reabsorption in the renal tubules is reduced, and more sodium stays in the tubular lumen to be excreted. It can also reduce the secretion of aldosterone, further inhibiting the reabsorption of sodium by the distal renal tubules and collecting ducts. Ang1–7 inhibits inflammatory reactions by reducing the release of pro-inflammatory cytokines (such as IL-6 and TNF-α), inhibiting myocardial hypertrophy and fibrosis, improving the survival environment of myocardial cells, and protecting myocardial function [22]. Studies have shown that the activation of the ACE2/Ang1–7/Mas axis can significantly reduce the levels of inflammatory markers in patients with hypertension, thereby improving vascular function and structure, reducing left ventricular hypertrophy, and reducing inflammatory reactions and ventricular remodeling.

2.2.2 Coronary atherosclerotic heart disease

In the study of coronary atherosclerosis, the classical RAAS ACE/Ang II/AT1R axis plays a crucial role. This axis promotes the occurrence and development of atherosclerosis through various mechanisms, including oxidative stress, inflammatory reactions, smooth muscle cell proliferation, and extracellular matrix remodeling [31].

Firstly, Ang II is the core effector molecule of the ACE/Ang II/AT1R axis, which activates multiple downstream signaling pathways by binding to its receptor, the angiotensin II type 1 receptor (AT1R). The most critical of these is the oxidative stress response mediated by NADPH oxidase. After binding with AT1R, Ang II activates NADPH oxidase through G protein signal transduction, increasing the production of reactive oxygen species (ROS). ROS further causes endothelial cell dysfunction, increases the permeability of endothelial cells, promotes the oxidation of low-density lipoprotein (LDL), and thus accelerates the formation of atherosclerotic plaques [32]. Secondly, Ang II significantly enhances inflammatory reactions through the NF-κB signaling pathway activated by AT1R. NF-κB is a key transcription factor that plays a central role in inflammation and immune responses. Ang II stimulates the activation of NF-κB, leading to an increase in the expression of inflammatory factors such as IL-6, TNF-α, and MCP-1 [33]. These inflammatory factors further promote the recruitment and adhesion of monocytes, promoting the formation of foam cells and accelerating plaque instability. In addition, Ang II can promote the proliferation and migration of vascular smooth muscle cells (VSMCs) through AT1R. The specific mechanism includes activating the ERK1/2 and p38 MAPK signaling pathways, as well as inducing the expression of early response genes such as Egr-1 and Fos, ultimately leading to the phenotypic transformation of VSMCs from the contractile type to the secretory type. Secretory VSMCs secrete cytokines and growth factors (such as

TGF-β) that can further stimulate the synthesis and deposition of the extracellular matrix, leading to thickening and hardening of the arterial wall. In addition, the ACE/Ang II/AT1R axis also stimulates the secretion of matrix metalloproteinases (MMPs) by endothelial cells and macrophages, causing matrix degradation and vascular remodeling. This process increases the vulnerability of atherosclerotic plaques, making them prone to rupture and thrombosis, thereby inducing acute coronary syndrome [34].

It is worth noting that in addition to the classic AT1R-mediated effects, there is a complex interaction between the ACE2/Ang-(1–7)/Mas axis. The ACE2/Ang-(1–7)/Mas axis plays a role in coronary atherosclerosis through several main mechanisms: 1. Anti-inflammatory effect: Studies have shown that Ang-(1–7) can inhibit the activation of the NF-κB pathway through the Mas receptor, reducing the expression of pro-inflammatory factors such as TNF-α and IL-6, thereby reducing inflammatory reactions. In addition, Ang-(1–7) can also reduce the infiltration of inflammatory cells in the plaque by inhibiting the activation and recruitment of macrophages to the plaque site, thereby lowering the inflammatory state of the plaque. 2. Antioxidant stress: Oxidative stress is an important factor in the occurrence and development of coronary atherosclerosis. Ang-(1–7) can promote the expression of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, through the Mas receptor-mediated pathway, thereby clearing free radicals and reducing the damage of oxidative stress to vascular endothelial cells and vascular smooth muscle cells. 3. Antiproliferation and anti-fibrotic effects: Ang-(1–7) can inhibit the proliferation and migration of vascular smooth muscle cells through the Mas receptor-mediated signaling pathway, thereby reducing vascular remodeling and plaque formation. In addition, Ang-(1–7) can also reduce the generation and fibrosis of the extracellular matrix by inhibiting the transforming growth factor-beta (TGF-β) and its downstream signaling pathways, thus playing a potential role in the prevention and treatment of coronary atherosclerosis. 4. Vasodilation and improvement of endothelial function: Ang-(1–7) can promote the release of nitric oxide (NO) through the Mas receptor, leading to the relaxation of vascular smooth muscle and improving blood flow dynamics, reducing vascular resistance. In addition, Ang-(1–7) can also improve endothelial cell function, promoting vascular repair and regeneration, thus playing a protective role in coronary atherosclerosis [35].

Although the role of the ACE2/Ang-(1–7)/Mas axis in coronary atherosclerosis has been widely studied, it still faces challenges in clinical application. Currently, several treatment strategies are being explored, including: 1. Ang-(1–7) analogs: The development of stable analogs or receptor agonists of Ang-(1–7) to enhance the protective effect of the ACE2/Ang-(1–7)/Mas axis and delay or reverse the progression of coronary atherosclerosis. These analogs can be delivered through subcutaneous injection, oral administration, or other methods, and research results show that these analogs have good efficacy in animal models. 2. ACE2 enhancers: Increasing the expression or activity of ACE2 through gene therapy or drug intervention to enhance the generation of Ang-(1–7) and play an anti-atherosclerotic role. Recent studies have shown that the exogenous delivery of the ACE2 gene can significantly reduce plaque area and inflammatory reactions in animal models of atherosclerosis. 3. Mas receptor agonists: The development of selective agonists for the Mas receptor to directly activate the downstream signaling pathway of Ang-(1–7), thereby playing an anti-inflammatory, anti-fibrotic, and vascular function improvement role. Several Mas receptor agonists are currently in preclinical research and show potential therapeutic effects. 4. Combined therapy: Considering the opposing roles of the ACE/Ang II/AT1R axis and the ACE2/

Ang-(1–7)/Mas axis in regulating vascular function, some studies have proposed the use of ACE inhibitors or Ang II receptor blockers (ARBs) in combination with ACE2/Ang-(1–7)/Mas axis-related drugs to further enhance the anti-atherosclerotic effect. This combined therapy strategy has shown a certain synergistic effect in clinical research.

In summary, the ACE2/Ang-(1–7)/Mas axis, as a potential therapeutic target for coronary atherosclerosis, has a broad application prospect. However, research on its specific molecular mechanisms and treatment plans still needs further in-depth, especially in large-scale clinical trials.

2.3 Endocrine system

Endocrine system diseases, such as diabetes, Cushing's syndrome, pheochromocytoma, and primary aldosteronism, play a crucial role in the renin-angiotensin system (RAS), especially the molecular mechanisms of the ACE/Ang II/AT1R axis and the ACE2/Ang-(1–7)/Mas axis and their impact on disease progression. With in-depth research on these diseases, people are increasingly recognizing that these two axes represent the pathogenic and protective pathways of the RAS, and their mechanisms of action and potential treatment strategies in various endocrine disorders have become hot topics of current research.

2.3.1 Diabetes

Diabetes is a chronic metabolic disease characterized by hyperglycemia. The ACE/Ang II/AT1R axis plays a key role in the pathogenesis of diabetes. Studies have shown that Ang II interacts with the insulin signaling pathway through AT1R, and leading to the exacerbation of insulin resistance and the apoptosis of pancreatic β-cells. Specifically, Ang II inhibits the IRS-1/PI3K/Akt signaling pathway, disrupting insulin-mediated glucose transport, leading to increased blood glucose levels. In addition, Ang II can also promote the functional decline of β-cells by promoting oxidative stress and inflammatory reactions within β-cells, thereby exacerbating the condition of diabetes. In diabetic nephropathy (DKD), the overactivation of the ACE/Ang II/AT1R axis is the main cause of glomerulosclerosis and interstitial fibrosis of the kidney. Ang II stimulates the proliferation of mesangial cells and the synthesis of extracellular matrix, leading to the occurrence of glomerulosclerosis. In addition, Ang II also promotes the expression of transforming growth factor-beta (TGF-β), promoting the process of interstitial fibrosis. These pathological changes ultimately lead to a decrease in glomerular filtration function, and severe cases can develop into end-stage renal disease (ESRD) [36]. In diabetes, the protective role of the ACE2/Ang-(1–7)/Mas axis is particularly important. Studies have shown that Ang-(1–7) can improve insulin signal transduction through the Mas receptor-mediated effect, reducing insulin resistance. In addition, Ang-(1–7) promotes the generation of nitric oxide (NO), improves endothelial function, and reduces oxidative stress and inflammatory reactions, thereby reducing vascular damage and complications related to diabetes. In diabetic nephropathy, the activity of the ACE2/Ang-(1–7)/Mas axis counteracts the glomerulosclerosis and interstitial fibrosis caused by the ACE/Ang II/AT1R axis. The specific mechanism includes inhibiting the expression of TGF-β, reducing the deposition of extracellular matrix, and maintaining the integrity of kidney structure by inhibiting the proliferation of mesangial cells [37]. Increasing the expression of ACE2 or directly applying Ang-(1–7) analogs is considered a potential strategy for treating diabetic nephropathy. In drug treatment, ACE inhibitors and AT1R antagonists can significantly improve the

metabolic state and kidney function of patients by improving insulin sensitivity and slowing the progression of diabetic nephropathy. Especially in patients with diabetic nephropathy, these drugs have become part of the standard treatment to delay the decline of kidney function and reduce proteinuria. In addition to traditional drugs, Dapagliflozin is a selective SGLT2 inhibitor that reduces the reabsorption of glucose by the kidney, thereby lowering blood glucose levels. In addition to its blood-lowering effect, Dapagliflozin also shows a protective effect on the cardiovascular system, especially in diabetic patients. The cardiovascular protective effect of Dapagliflozin is partly related to its regulation of the RAS [35]. Studies have shown that Dapagliflozin can balance the ACE/Ang II/AT1R axis and the ACE2/Ang-(1–7)/Mas axis by reducing the generation of Ang II or enhancing the expression of ACE2, thereby reducing inflammatory reactions, oxidative stress, and fibrosis. These effects are important for preventing cardiovascular complications in diabetic patients, especially heart failure and kidney damage [38]. In clinical practice, Dapagliflozin has been proven to significantly reduce the incidence of cardiovascular events in diabetic patients and delay the progression of diabetic nephropathy. Due to its multiple mechanisms of action, Dapagliflozin is considered a very promising drug for the treatment of diabetes and its complications. In addition to ACE inhibitors, AT1R antagonists, and SGLT2 inhibitors, other drugs targeting the RAS are also showing potential in the treatment of endocrine diseases. For example, direct renin inhibitors (such as Aliskiren) inhibit the activity of renin, reducing the generation of Ang I and Ang II, thereby inhibiting the activity of the RAS. Although the clinical application of these drugs is still being explored, their potential therapeutic value should not be overlooked.

2.3.2 Cushing's syndrome

Cushing's syndrome is an endocrine disease caused by excessive secretion of glucocorticoids. The role of the ACE/Ang II/AT1R axis in Cushing's syndrome is increasingly being paid attention to. Glucocorticoids enhance the activity of the RAAS, especially the activity of the ACE/Ang II/AT1R axis, by upregulating the expression of ACE, increasing the generation of Ang II, and causing a series of adverse reactions through AT1R, including hypertension, insulin resistance, lipid metabolism disorders, and cardiovascular complications. Excessive secretion of glucocorticoids can enhance the activity of the RAAS, especially the activity of the ACE/Ang II/AT1R axis. Ang II causes hypertension in patients with Cushing's syndrome mainly through the vasoconstriction and sodium retention effects mediated by AT1R. In addition, Ang II can also accelerate the progression of atherosclerosis and the increase of cardiovascular events through the oxidative stress pathway. At the metabolic level, Ang II can promote the ectopic deposition of fat by disrupting the function of adipose tissue, thereby exacerbating insulin resistance and glucose metabolism disorders [39]. There is limited research on the ACE2/Ang-(1–7)/Mas axis in Cushing's syndrome, but existing evidence suggests that this axis may play a role in alleviating metabolic disorders and cardiovascular complications caused by excessive glucocorticoids [40]. Ang-(1–7) may counteract the pathogenic effects of the ACE/Ang II/AT1R axis in Cushing's syndrome through its anti-inflammatory and antioxidant effects. In Cushing's syndrome, the expression of ACE is upregulated by glucocorticoids, leading to increased activity of the ACE/Ang II/AT1R axis. Therefore, regulating the activity of the ACE2/Ang-(1–7)/Mas axis to restore the balance of the RAAS may be a promising direction for treatment [41]. Future research needs to further explore the specific mechanisms of this axis in Cushing's syndrome and its therapeutic potential.

2.3.3 Pheochromocytoma and primary aldosteronism

Pheochromocytoma and primary aldosteronism are two common causes of endocrine hypertension. The ACE/Ang II/AT1R axis shows significant activation in these diseases, leading to a marked increase in blood pressure. In pheochromocytoma, due to the secretion of a large amount of catecholamines by tumor cells, the overactivation of the sympathetic nervous system leads to an enhancement of RAAS activity, especially the activity of the ACE/Ang II/AT1R axis. Ang II further exacerbates vasoconstriction and blood pressure increase through the effects of AT1R. In addition, Ang II can also promote the secretion of aldosterone, leading to sodium retention and excessive body fluid, aggravating the degree of hypertension.

Primary aldosteronism is a disease caused by the overproduction of aldosterone by the adrenal cortex. Its main features are refractory hypertension and hypokalemia. Aldosterone leads to an increase in blood volume and elevated blood pressure by increasing sodium reabsorption by the kidney. At the same time, aldosterone can also enhance the activity of the ACE/Ang II/AT1R axis by upregulating the expression of ACE. Ang II, through the vasoconstrictive effects mediated by AT1R as well as by promoting fibrosis and oxidative stress, further exacerbates cardiovascular complications, such as left ventricular hypertrophy and arteriosclerosis. In pheochromocytoma and primary aldosteronism, the role of the ACE2/Ang-(1–7)/Mas axis is also of interest. Studies have shown that Ang-(1–7) can lower blood pressure and reduce cardiovascular complications associated with hypertension through the Mas receptor [42]. In pheochromocytoma, Ang-(1–7) reduces hypertension and cardiovascular complications caused by excessive secretion of catecholamines by inhibiting the pathogenic effects of the ACE/Ang II/AT1R axis. In addition, Ang-(1–7) can also reduce cardiac remodeling and heart failure commonly seen in patients with pheochromocytoma through its anti-fibrotic effects. Studies have found that enhancing the expression of ACE2 or directly applying Ang-(1–7) analogs can significantly improve blood pressure control and cardiovascular prognosis in patients with primary aldosteronism [43]. ACE inhibitors and AT1R antagonists are widely used to control hypertension. By inhibiting the effects of Ang II, these drugs not only effectively lower blood pressure but also reduce the incidence of cardiovascular complications. Especially for patients who cannot undergo surgery, these drugs provide an important noninvasive treatment option. Surgical removal is the preferred method for treating pheochromocytoma, which can usually cure hypertension and other related symptoms completely. Before surgery, patients usually need to control blood pressure with medication to prevent perioperative crises caused by excessive release of catecholamines. Preoperative preparation usually includes the use of alpha-blockers (such as phenoxybenzamine) and beta-blockers (such as propranolol) to stabilize blood pressure and heart rate. In addition, emotional excitement and other factors that may induce the release of catecholamines should be avoided before surgery. After the tumor is removed, most patients' hypertension can be significantly improved or even completely resolved. However, blood pressure and catecholamine levels still need to be monitored after surgery to prevent tumor recurrence or residue [44]. In addition, long-term follow-up after surgery is also crucial for assessing cardiovascular health and preventing complications [45]. Primary aldosteronism is a disease caused by the overproduction of aldosterone by the adrenal cortex, and its main features are refractory hypertension and hypokalemia. Surgical treatment is usually aimed at adrenal cortical adenomas or hyperplasia, and it can restore normal aldosterone levels by removing the affected tissue [36]. For patients with unilateral adrenal adenomas, laparoscopic adrenalectomy

is the preferred method. This minimally invasive surgery has a small trauma and fast recovery, and can significantly improve patients' blood pressure and potassium metabolism [46]. Before surgery, patients usually need to control blood pressure and electrolyte balance with medication to reduce complications during and after surgery [47]. For patients with bilateral adrenal hyperplasia, the choice of surgical treatment is more complex and may require individualized treatment based on the patient's specific situation. Long-term follow-up is still needed after surgery to monitor blood pressure and aldosterone levels and adjust drug treatment plans as needed.

2.4 Renal system

Diseases of the renal system are a common group of chronic diseases, among which glomerular diseases, diabetic nephropathy (DN), hypertensive nephropathy (HN), and others are the main types of diseases. The pathogenesis of these diseases is complex and closely related to multiple molecular signaling pathways. The renin-angiotensin system is an important system for regulating renal hemodynamics, salt and water balance, and blood pressure, and its dysregulation plays a key role in the pathological process of kidney diseases.

2.4.1 Diabetic nephropathy

Clinically, acute kidney injury (AKI) is considered a catastrophic disease with high incidence and mortality rates. One of the main risk factors for AKI is diabetes mellitus (DM). Compared with non-diabetic patients, diabetic patients are still at a higher risk of developing AKI [48]. The poor renal outcomes of DM and AKI are mainly attributed to apoptosis, inflammation mediated by NF-κB, and oxidative stress promoted by the renin-angiotensin system (RAS) through mitogen-activated protein kinase (MAPK) [49]. Therefore, inhibiting the RAS with angiotensin II receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEi) is considered to prevent AKI. Surprisingly, when ARBs and ACEi are used to treat AKI patients, they increase the severity of AKI. This highlights the need for new treatment methods for AKI [35]. The ACE/Ang II/AT1 axis has been deeply explored in the pathophysiology and drug treatment of renal complications, including AKI. However, to date, the role of the ACE2/Ang-(1–7)/Mas axis in the pathogenesis of AKI-DM comorbidity has been little studied. The ACE2/Ang-(1–7)/Mas axis establishes compensatory mechanisms by sensing increased cellular stress and pathological signals, which are beneficial to the renal system. Mice with distal renal injury induced by tourniquet show a disorder of ACE and ACE2 activity, which can lead to kidney damage. Interestingly, restoring the ACE/ACE2 balance by upregulating ACE2 can prevent renal injury. Studies have shown that lipopolysaccharide-induced endotoxemia significantly reduces ACE2 mRNA levels: subsequently, the levels of Ang II and inducible nitric oxide synthase in the kidney are increased, while restoring ACE2 levels can maintain endothelial pore size, glomerular filtration rate, and proximal renal tubular function, ultimately protecting the kidney from AKI. Ruiz-Ortega and others have demonstrated that AT2R is overexpressed in Balb/c renal tubular cells under treatment with folic acid-induced AKI and have put forward the potential role of AT2R in protecting kidney damage [38]. Subsequently, overexpression of AT2R and activation of ACE2 activity significantly improved renal function in these models of mice. Recently, Nisha Sharma and others have shown that inhibiting the ACE2/Ang-(1–7)/Mas axis can induce ischemic AKI in non-diabetic (ND) and streptozotocin-induced diabetic (DM) rats and found

that the severity of ischemic AKI is widespread in DM rats, which may be due to the presence of hyperglycemia damage [50]. A new combined therapy targeting the RAAS protective axis with AT2R agonists and ACE2 activators can significantly alleviate systemic and renal RAS changes and prevent renal tubular injury related to IRI in ND and DM rats [51]. Therefore, targeting the ACE2/Ang-(1–7)/Mas axis may be a new therapeutic option for AKI.

2.4.2 Hypertensive nephropathy

Hypertension affects about 30% of the general population. Hypertensive nephropathy is considered one of the complications of long-term and poorly controlled hypertension. Hypertensive nephropathy is the second leading cause of end-stage renal disease (ESRD) after diabetes. Most patients with hypertension will develop mild to moderate hypertensive nephrosclerosis [52]. However, when blood pressure (BP) values are not controlled for a long time or when there is a pre-existing kidney disease, the proportion of patients developing ESRD will increase sharply [53]. For a long time, attention has been paid to renal fibrosis and hyaline degeneration caused by the injury to the glomerular tuft, as well as the activity of the RAS system. However, recently, molecular mechanisms and other histological aspects have been included in the pathophysiology of hypertensive nephropathy, including renal tubular cell injury leading to epithelial-mesenchymal transition (EMT) and renal interstitial fibrosis. Angiotensin II promotes renal oxidative stress and mediates epithelial-mesenchymal transition through the AT1-ERK/mitogen-activated protein kinase (MAP) kinase, TGF-β/Smad2/3, and NF-κB pathways. One of the protective mechanisms of cells against oxidative stress is the production of highly conserved proteins called heat shock proteins (Hsps). Hsps are intracellular proteins that respond to cellular stress and act as chaperon proteins for other "client" peptides, binding to these peptides to prevent their irreversible aggregation and promoting their correct folding, physiological assembly, and intracellular transport. In addition to traditional ACE inhibitors and Ang II receptor blockers (ARBs), treatment strategies based on the ACE2/Ang-(1–7)/Mas axis mainly focus on the development of ACE2 and Mas receptor agonists. ACE2 agonists can inhibit the pathogenic effects of Ang II by increasing the generation of Ang-(1–7) [54]. Currently, ACE2 agonists have shown good renal protective effects in animal models, but their clinical application still needs further verification. Mas receptor agonists play an anti-inflammatory, anti-fibrotic, and antioxidant stress role by directly activating the Mas receptor. The therapeutic potential of these drugs in kidney diseases is also being widely studied. The ACE/Ang II/AT1 axis and the ACE2/Ang-(1–7)/Mas axis play a pathogenic and protective role in hypertensive nephropathy, respectively. With an in-depth understanding of these two signaling axes, more effective treatment strategies can be developed. At present, ACE inhibitors and ARBs have been widely used in clinical practice, and ACE2 and Mas receptor agonists represent a new direction for the treatment of kidney diseases in the future. With in-depth research, these emerging therapies are expected to provide better treatment options for patients with kidney system diseases [55].

2.4.3 Invasive treatment of ACE/Ang II/AT1 axis and ACE2/Ang-(1: 7)/mas axis

The ACE/Ang II/AT1 axis and the ACE2/Ang-(1–7)/Mas axis play a key role in the invasive treatment of the renal system. These axes not only affect the pathological process of the disease but also guide the implementation of certain invasive treatments and their postoperative management.

Renal artery stenosis (RAS) is one of the main causes of renal hypertension and renal insufficiency. The activation of the ACE/Ang II/AT1 axis in RAS leads to a reduction in renal blood flow, which in turn triggers systemic hypertension and renal damage. In this case, renal artery interventional treatment (such as percutaneous renal artery angioplasty or stent implantation) is a commonly used invasive treatment method. This treatment reduces Ang II levels by improving renal artery blood flow, and reducing the pathogenic effects of AT1 receptor-mediated vasoconstriction, inflammation, and fibrosis [56]. Before and after surgery, ACE inhibitors or Ang II receptor blockers (ARBs) are often used in the clinic to further control the activity of the ACE/Ang II/AT1 axis, preventing postoperative hypertension rebound and renal function deterioration. For patients who fail to effectively control blood pressure after surgery, ACE2 agonists and Mas receptor agonists may become potential adjuvant treatment options, further counteracting the harmful effects of Ang II by enhancing the activity of the ACE2/Ang-(1–7)/Mas axis [57].

In patients with end-stage renal disease (ESRD), renal transplantation is the most effective invasive treatment method. However, the transplanted kidney often suffers from acute injury and rejection reactions during reperfusion, and the overactivation of the ACE/Ang II/AT1 axis often exacerbates the damage to the transplanted kidney [58]. Ang II can lead to acute injury and long-term fibrosis of the transplanted kidney by promoting vasoconstriction and inflammation. To reduce these adverse reactions, ACE inhibitors or ARBs are usually required after transplantation to inhibit the activity of the ACE/Ang II/AT1 axis, thereby protecting the function of the transplanted kidney. In addition, the ACE2/Ang-(1–7)/Mas axis also has potential effects in protecting the transplanted kidney after transplantation. ACE2 may help reduce reperfusion injury and inflammatory reactions by reducing the generation of Ang II and increasing the generation of Ang-(1–7). Mas receptor agonists, as a new treatment strategy, may improve the long-term prognosis of the transplanted kidney by activating protective pathways [59]. Hemodialysis treatment, is an important treatment for end-stage renal disease, although not a direct invasive treatment for the kidney, the balance of the ACE/Ang II/AT1 axis and the ACE2/Ang-(1–7)/Mas axis is still crucial during the maintenance of hemodialysis [60]. Hemodialysis patients often have hypertension and cardiovascular diseases, which are closely related to the abnormal activity of the ACE/Ang II/AT1 axis. The use of ACE inhibitors or ARBs can effectively control blood pressure in hemodialysis patients and reduce the incidence of cardiovascular complications.

In summary, the regulation of the ACE/Ang II/AT1 axis and the ACE2/Ang-(1–7)/Mas axis in the invasive treatment of the renal system is of great significance. These axes not only affect the pathological process of the disease but also play a key role in postoperative management and long-term prognosis. In the future, more precise treatment strategies targeting these two signaling axes will further improve the treatment effects for patients with renal diseases.

3. Conclusions

As our understanding of the RAAS system deepens, there is potential for the development of more targeted drugs with fewer side effects. For instance, medications targeting the ACE2/Ang-(1–7)/Mas axis may aid in the treatment of hypertension and diabetic nephropathy. Personalized treatment plans could also be provided based on a patient's genotype and phenotype. For example, the selection of the most appropriate medication could be based on the patient's RAAS gene polymorphisms. Combined therapies that utilize drugs targeting different axes of the RAAS might

produce synergistic effects, enhancing therapeutic outcomes. An example of this is the combined use of ACE inhibitors or ARBs with ACE2 agonists.

Despite current advancements in RAAS system research, the long-term use of RAAS inhibitors may lead to the development of tolerance in patients, and certain drugs may cause side effects such as coughing and hyperkalemia. Additionally, there are variations in patient responses to RAAS inhibitors that require further research to elucidate the causes of this heterogeneity. The high cost of new drug development poses a significant challenge in balancing the efficacy, safety, and economic cost of medications. Particularly, the interactions among the various components within the RAAS system are highly complex, making it difficult for a single drug to regulate the entire system comprehensively.

In summary, research and development of therapeutic strategies for the RAAS system is a field replete with challenges and opportunities. Future research needs to build upon a profound understanding of the RAAS system to develop novel treatment methods while addressing the limitations of existing therapeutic approaches. Through interdisciplinary collaboration, personalized medicine, and consideration of social ethics, more effective and safer treatment options can be provided for patients.

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Conflict of interest

The authors declare no conflict of interest.

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