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Therapeutic Potential of RAS Inhibitors in the Management of Diabetes

Mingyang Luo[1,a,*]

[1]*College of pharmacy, Harbin Medical University, 150081, China*
a. 2022141066@hrbmu.edu.cn
**corresponding author*

Abstract: The global prevalence of diabetes is on the rise, with its pathogenesis closely related to the renin-angiotensin system (RAS) that includes the classical antagonistic pathway and the ACE2-Ang-(1-7)-Mas axis. Despite its well-documented role in cardiovascular health, the potential mechanisms by which RAS is associated with diabetes require further study. RAS interacts with metabolic regulatory factors such as obesity and autophagy. Excessive activation of the Ang II-AT1 receptor pathway can contribute to insulin resistance and diabetic complications. This review elucidates the mechanisms by which RAS contributes to diabetes development and discusses both clinical applications and future directions for RAS inhibitory drugs in managing diabetes. And it concludes that RAS inhibitors hold significant promise for treating diabetes and its associated complications, warranting deeper exploration into their future roles within this field. The results indicate the intricate relationship between RAS and diabetes, alongside the therapeutic potential offered by RAS inhibitors.

Keywords: RAS Inhibitors, Diabetes, Drug Combination, Clinical Application

1. Introduction

Diabetes mellitus is a chronic metabolic disorder characterized primarily by insulin resistance coupled with inadequate insulin secretion. Recently, there has been a notable increase in incidence rates globally, prompting numerous countries to prioritize addressing this public health challenge through effective interventions. The renin-angiotensin system (RAS) plays a pivotal role in regulating blood pressure as well as fluid and electrolyte balance [1]. The classical components of the system include renin, angiotensin-converting enzyme (ACE), angiotensin II (Ang II), along with its receptors, thus forming an interconnected linear cascade. The significance of RAS in cardiovascular physiology is well-documented. However, it also serves multiple functions including involvement in adipogenesis while exerting differential effects on autophagy across various tissues, thus influencing glucose homeostasis. And excessive activation may lead to metabolic syndrome manifestations such as diabetes itself. This review synthesizes recent findings regarding how alterations within RAS are implicated in metabolism-related disorders like diabetes while highlighting evidence that supports using RAS inhibitors effectively ameliorating these conditions along with their complications. Furthermore, it explores synergistic effects when combining these agents with traditional antidiabetic medications, a consideration for optimizing clinical treatment strategies moving forward, as well as identifying promising avenues for research focused on leveraging ACE2 pathways within drug development aimed at combating diabetes.

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2. Overview of the RAS system

The RAS constitutes an essential component of human endocrine regulation. In the classical pathways of this system, angiotensinogen (Agt) acts as a precursor transformed into Ang I and Ang II via enzymatic action from renin, which is then converted by ACE [2]. Ang II emerges as a principal bioactive peptide whose physiological impacts are mediated predominantly through two G protein-coupled receptors: type 1 angiotensin receptor (AT1R or AGTR1) and type 2 receptor (AT2R or AGTR2) [2]. Engagement of Ang II at AT1 receptors triggers adverse biological responses including inflammation induction, oxidative stress elevation, vasoconstriction among others detrimental processes affecting overall health outcomes [3]. In addition to the classical RAS, the ACE2-Ang-(1-7)-Mas axis functions as a negative regulator of RAS. Ang-(1-7) is generated from Ang I by ACE2 and interacts with both the AT2 receptor and the G protein-coupled MAS receptor, exerting effects that are fundamentally opposite to those mediated by the Ang II pathway. These include inhibiting Ang II-induced vasoconstriction, as well as the promotion of growth inhibition, anti-arrhythmic activity, and antithrombotic effects, thereby providing protective benefits for the organism and indicating its potential as a target for novel drug development. The antagonistic actions of these two systems are crucial for maintaining homeostasis within the body's internal environment [4]. At present, drugs acting on the RAS are collectively termed as RAS inhibitory drugs, whose main function is to inhibit the Ang2-AT1 pathway. And they can be classified as renin inhibitors, ACEIs, and ARBs. The most typical drug for renin inhibitors is orally available aliskiren, which can block the renin system at the source and thereby inhibit the production of the active peptide Ang II [5]. Furthermore, ACEIs and ARBs are the most commonly used RAS inhibitory drugs in clinical practice, which inhibit ACE activity and the binding of ligands to the AT1 receptor respectively [6]. However, studies have shown that the effect of ARBs is due to the selectivity for the AT1 receptor, combined with the almost opposite effect of the AT2 receptor agonist on blood vessels, raising the following possibility: Some of the benefits of ARBs may come from the increased activation of the AT2 receptor, rather than just from the blockade of the AT1 receptor [7].

3. The Role of the RAS System in Metabolic Regulation

3.1. RAS and Obesity

Obesity significantly influences the RAS, as evidenced by elevated plasma levels of AGT, renin, ACE, and aldosterone. Adipose tissue serves as the primary source of AGT, and obesity induces alterations in both the expression and secretion of various RAS components within this tissue [8]. In addition, the RAS impacts adipocyte differentiation and function, in which local or circulating Ang II exerts a negative regulatory effect on adipocyte differentiation through activation of extracellular signal-regulated kinase (ERK) within the mitogen-activated protein kinase (MAPK) signaling pathway via type 1 receptor (AGTR1) [9]. Experimental studies have shown that AGTR1 knockout rats exhibit improved outcomes related to diet-induced obesity, including enhanced lipolysis and increased fatty acid oxidation [10]. In contrast, recent research indicates that the ACE2-Ang-(1-7)-Mas axis plays a crucial role in both the onset and progression of obesity. Ang-(1-7) activates Akt and PKA signaling pathways, promotes UCP1 expression, and enhances mitochondrial function, thereby facilitating thermogenesis and energy metabolism in brown adipose tissue (BAT), which may ameliorate obesity while representing a potential therapeutic target for metabolic disorders [11]. In obese patients, hyperactivation of the classical RAS pathway mediated by Ang II/AGTR1 correlates with hypertension induced by obesity, insulin resistance, and inflammation. This phenomenon arises in that heightened RAS activity triggers activation of the nuclear factor κB (NF-κB) pathway, leading to an increase in pro-inflammatory cytokines production [12]. Besides, Ang II upregulates glycerol-

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3-phosphate dehydrogenase (a key lipogenic enzyme in adipocytes), leading to triglyceride accumulation in adipose tissue and even adipocyte hypertrophy, accompanied by infiltration from pro-inflammatory M1 macrophages. These macrophages further stimulate the release of pro-inflammatory cytokines, thus perpetuating the vicious cycle. Thus, chronic or intermittent cold exposure constitutes a risk factor for hypertension as well as cardiovascular diseases. Cold stimulation can induce cold-induced hypertension (CIH) via mechanisms involving the RAS. Additionally, Ang II may play an integral role in regulating cold-induced thermogenesis associated with hypertension linked to obesity among other pathologies [13]. And the interaction between obesity and RAS contributes to the development of obesity and its associated metabolic complications through multiple mechanisms.

3.2. RAS and Autophagy

Autophagy plays a vital role in the survival of cells by recycling and degrading cellular waste and aging cells through subcellular processes involving lysosomes and vacuoles, particularly providing nutrients for cells under starvation[14]. The RAS can also act locally though it functions mainly throughout the body. Porrello et al. found a relationship between the RAS and autophagy in cardiomyocytes, indicating that the interaction between Ang2 and the AT1 receptor increases the formation of autophagosomes; conversely, when Ang2 interacts with AT2, it antagonizes the autophagy-inducing function of the AT1 receptor [15]. Unlike Ang II, which is positively correlated with autophagy, Ang 1-7 has a negative correlation with autophagy. Similarly, the Ang1-7/MAS pathway inhibist the formation of autophagy. Relevant studies have shown that treatment with Ang 1-7 infusion can effectively reduce the levels of autophagy markers such as LC3-II and Beclin 1 in mice [16]. Lin et al. showed that the anti-autophagy effect of Ang 1-7 in cardiomyocytes was achieved by inhibiting the autophagy, hypertrophy, and oxidative stress stimulated by Ang II, thus providing a protective function in cardiomyocytes [17]. However, another study presented an opposite finding related to Ang 1-7, where Ang 1-7 does not inhibit autophagy but induces autophagy via cofilin-1 expression in human aortic endothelial cells (HAEC) [18]. Currently, studies on the relationship between the RAS and autophagy in adipose tissue are unclear. It has been shown that autophagy in adipose tissue may be achieved via the pro-inflammatory function of Ang II and RAS-related cellular stress (oxidative stress, ER stress) [19]. The study by Yadav et al. in mouse podocytes revealed that Ang II induces autophagy via reactive oxygen species (ROS) generation. Antioxidants can inhibit Ang II-induced autophagosomes formation in these podocytes [20]. Both Ang2-induced ROS and the pro-inflammatory pathways caused by the overexpression of RAS may both be triggers of autophagy. Meanwhile, ROS may have a direct inhibitory effect on the PI3K/Akt pathway (which inhibits autophagy by activating mTOR or suppressing FoxO expression). Though RAS overexpression in adipose tissue may activate autophagy, its specific mechanism remains to be further explored to reveal the role of angiotensin in the autophagic process.

4. Clinical application of RAS inhibitors in the treatment of diabetes mellitus

4.1. Enhancement of Insulin Sensitivity through RAS Inhibitors

A hallmark of diabetes is insulin resistance, which is often linked to the overexpression of the RAS. Under physiological conditions, there is a mutually regulated balance between the insulin signaling pathway and the RAS. Ang II regulates insulin secretion by activating AT1R on the surface of β-cells. Conversely, insulin influences both central and local RAS components via its receptors, enzymes, and effector peptides. However, in states of RAS hyperactivation, enhanced AT1 receptor activity and increased aldosterone production can obstruct insulin signal transduction pathways, thereby precipitating insulin resistance. Insulin acts through two primary pathways: the IRS/PI3K

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pathway that directly mediates metabolic actions of insulin and the MAPK pathway involved in non-metabolic functions [21]. Ang2 interference with IRS/PI3K signaling has been found to be an intrinsic mechanism of reduced insulin sensitivity. This disruption occurs in that Ang2-induced activation of AT1 receptors leads to ROS generation, which activates various kinases and leads to the inactivation of IRS-1 [22]. Furthermore, ANGII impedes adipocyte differentiation, promoting visceral fat accumulation which contributes to the development of insulin resistance alongside unregulated lipolysis, and triggers inflammation, dyslipidemia, hypertension, and hyperglycemia [23,24]. Thus, insulin resistance is further exacerbated by dysfunctional adipocytes with enhanced lipolysis and pro-inflammatory features. Meanwhile, this state alters pancreatic islet structure with a compensatory increase in insulin secretion accompanied by an upregulation of components within the RAS, creating a vicious cycle that explains renal and cardiovascular dysfunction in diabetic patients [25].

The relationship between RAS and insulin resistance highlights the clinical potential of RAS inhibitors to ameliorate this condition. The primary role of these inhibitors is to attenuate the inhibitory effect of ANG2 while directly antagonizing the AT1 receptor to achieve therapeutic effects. To date, ACEIs and ARBs have been recognized as key strategies for disrupting RAS function. In addition, renin plays an integral role in this system; renin inhibitors (e.g., aliskiren) have been shown to be efficacious in improving insulin sensitivity in humans and animal models. However, it remains uncertain whether renin exerts a direct effect on, for example, improving glucose uptake, or whether it primarily affects downstream elements within the RAS framework (e.g., lowering Ang II or aldosterone levels) to enhance overall insulin sensitivity [26]. Treatment with captopril, a specific ACEI, has been shown to upregulate key components associated with RAS function and enhance muscle/liver autophagy processes, thus improving insulin sensitivity in diabetic or obese patients. Similarly, ARBs such as valacyclovir have been shown to reduce fasting blood glucose levels in hypertensive obese patients [27]. In addition to classical RAS inhibitors, there is another promising pathway, the ACE2/Mas receptor axis, which is targeted to address the problem of insulin sensitivity by converting Ang II to Ang (1-7), counteracting the deleterious interactions arising from the binding of ANG2 to AT1R.

4.2. The Role of RAS Inhibitors in the Management of Diabetic Complications

Ang II-induced insulin resistance exacerbates the risk of several metabolic complications as IR disrupts the IRS/PI3K signaling pathway, rendering insulin ineffective in regulating glucose homeostasis and other metabolic processes. At the same time, the MAPK signaling pathway remains intact, which facilitates even the non-metabolic effects of insulin, thus allowing it to affect tissues not directly involved in metabolism, with potentially deleterious outcomes such as arterial hypertension [28]. Hypertension observed in patients with insulin resistance is mainly attributed to excessive activation of the RAS due to insulin resistance-induced compensatory hyperinsulinemia. High insulin levels further stimulate the ACE/ANGII/AT1R axis in the vascular endothelium, exacerbating the hypertension characteristic of IR and obesity. In a state of insulin resistance, high levels of Ang II in the blood and tissues promote fibrotic, inflammatory and hypertrophic processes leading to remodeling and dysfunction of the cardiovascular and renal systems [29].

Diabetes may also increase the risk of neurodegenerative diseases. Long-term studies have shown that people with type 2 diabetes mellitus (T2DM) have twice the risk of dementia as non-diabetic populations, which may be related to abnormal diabetes-related insulin signaling in the brain [30,31]. In addition, the recent mouse study has found that diabetes and hypertension activate the RAS in the cerebral cortex, exacerbating neurological damage via AT1R expression, implying that individuals with both diabetes and hypertension are more susceptible to neurodegenerative changes [32]. Diabetes also alters cardiomyocyte protective mechanisms against ischemic injury (e.g., SAFE and RISK pathways), significantly increasing the heart's threshold for injury during an ischemic event,

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leading to the potential ineffectiveness of traditional protective strategies [33-35]. In addition, diabetes decreases the expression of the GLUT-4 transporter in cardiomyocytes, thereby increasing the risk of cell death [36].

Thus, the high levels of Ang II and AT1R expression upregulated under conditions of insulin resistance are a hallmark of pancreatic RAS dysregulation. This dysregulation causes chronic vasoconstriction, affects pancreatic blood flow, impairs functions related to insulin secretion, and ultimately leads to glucose intolerance. Disturbed insulin signaling coupled with elevated ANGII levels ultimately leads to metabolic syndrome and type 2 diabetes [37]. Relevant studies show that captopril and losartan, alone or in combination, attenuate acute hyperglycemia or STZ-induced ischemia/reperfusion (I/R) injury in diabetic hearts, improve cardiac hemodynamics, reduce infarct size, decrease apoptotic marker levels, and reduce pro-inflammatory cytokine concentrations. Notably, this protective effect was not related to ERK1/2 and eNOS activity, but was achieved by reducing apoptosis and enhancing anti-inflammatory factors, which may be related to the involvement of GLUT-4 [38]. The beneficial effects of RAS blockade on the control of metabolic syndrome (MetS) and prevention of diabetic complications are mainly due to its multiple mechanisms: reduction of inflammatory factor concentrations, enhancement of lipocalin secretion, improvement of endothelial function, facilitation of insulin-mediated glucose uptake, maintenance of pancreatic islet structural integrity, enhancement of fatty acid storage capacity, and inhibition of AT1R to minimize neurological damage.

4.3. Combined Use of RAS Inhibitors and Diabetes Medications

In combination therapy, the concurrent application of RAS inhibitors in conjunction with other pharmacological agents demonstrates the potential to enhance efficacy, minimize adverse effects, and ameliorate diabetic complications. Studies have shown thatthe combined treatment involving SGLT2 inhibitors (such as empagliflozin, canagliflozin, dapagliflozin) and RAS inhibitors markedly reduces cardiovascular and renal event risks in patients with diabetes. SGLT2 inhibitors exert their hypoglycemic effect through inhibition of renal glucose reabsorption and have multiple benefits in terms of lowering blood pressure, reducing body weight, and improving cardio-renal prognosis [39]. They exert hypoglycemic effects by inhibiting renal glucose reabsorption and have multiple benefits including lowering blood pressure, reducing body weight, and improving cardiac and renal prognosis. And this combination is superior to RAS inhibitors alone in preventing atherosclerotic cardiovascular events (ASCVD), heart failure (HF) and renal failure [41]. In addition, SGLT2 inhibitors reduce endogenous trophic factor levels, which may help slow the progression of kidney disease.

The triple combination of GLP-1 receptor agonists (e.g., liraglutide, semaglutide, dulaglutide), SGLT2 inhibitors, and RAS inhibitors offers additional advantages in the management of diabetes [42]. GLP-1 receptor agonists indirectly improve insulin sensitivity by enhancing insulin secretion, inhibiting glucagon, reducing hepatic glucose production, and suppressing appetite, addressing multiple causative factors of diabetes mellitus, where SGLT2 inhibitors reduce glucose toxicity by inhibiting renal tubular glucose reabsorption, thus improving insulin sensitivity and β-cell function [43]. The combination of multi-targeted synergistic effects is effective in lowering macrovascular and microvascular complications, improving cardiovascular risk, and preventing diabetic nephropathy. Moreover, calcium channel blockers (CCBs) or diuretics in combination with RAS inhibitors have shown significant efficacy in the control of hypertension in patients with diabetic kidney disease (DKD). Hypertension is prevalent in DKD patients and is strongly associated with increased urinary albumin excretion, which accelerates disease progression and increases the risk of renal failure. CCBs lower blood pressure by blocking the influx of calcium ions into vascular smooth muscle cells, while diuretics lower blood pressure by inhibiting sodium reabsorption. Recent studies show that combinations of RAS inhibitors in combination with diuretics or CCB are more efficacious and have

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fewer side effects than single agents [44]. However, the results of a recent meta-analysis suggest that ARB plus CCB combinations enhance protection against cardiovascular disease compared to ARB plus diuretic combinations [45].

Furthermore, steroidal mineralocorticoid receptor antagonists (e.g., spironolactone/epothilone) significantly reduce albuminuria when combined with RAS blockers. However, steroidal MRAs lead to a significant increase in serum potassium levels, stimulating the development of non-steroidal alternatives, such as fenorethisterone. The integration of this latter compound offers a promising avenue for the treatment of diabetic nephropathy, with a marked efficacy in the reduction of proteinuria and no adverse effects. In contrast, data from the FIDELIO-DKD trial and the FIGARO-DKD trial demonstrated minimal changes in aldosterone concentrations (+0.2 mEq/L) during 90 days of finerenone treatment, and the incidence of hyperkalemia remained low compared to placebo, emphasizing its good safety profile [47,48]. Thus, the newly developed MRA fenetyllone has a higher selective affinity for aldosterone receptors compared to traditional RAS antagonists, and a strategy that combines these two classes of drugs may improve the overall efficacy of targeting proteinuric states while decreasing the risk of hyperkalemia and mitigating a broader cardiovascular/renal threat [49]. At the same time, the combination of herbal medicines with RAS inhibitors is also a current trend. For example, the Cordyceps sinensis preparations or Salvia miltiorrhiza and chasteberry injections (SML) in combination with ACEI/ARB are beneficial for renal function in patients with DKD, reducing proteinuria, dyslipidemia and even oxidative stress and inflammation [50,51].

4.4. Future Research Directions and Clinical Prospects

RAS inhibitors, especially ACEI and ARBs, have been widely used in the treatment of diabetes mellitus and its related complications and have demonstrated significant clinical efficacy. In recent years, researchers have come to realize that activation of the ACE2/Ang-(1-7) (Ang-(1-7))/Mas receptor (MasR) axis may provide a novel mechanism for the treatment of diabetes with significant clinical potential. The role of the ACE2/Ang-(1-7)/Mas receptor axis in metabolic regulation has attracted much attention. This pathway improves diabetes control via multiple physiological mechanisms, including promoting pancreatic β-cell proliferation and insulin secretion, thus enhancing insulin sensitivity in skeletal muscle and adipose tissue, and decreasing hepatic glucose production [52]. Ang-(1-7), as a metabolite of ACE2, exerts protective effects by inhibiting the pro-inflammatory and pro-fibrotic effects of Ang II, and reduces Ang II-mediated vasoconstriction, oxidative stress, and inflammation by competitive binding to AT1 receptors via Mas receptors [53]. This dual mechanism makes the ACE2/Ang-(1-7)/Mas axis uniquely advantageous in diabetes management. At the mechanistic level, the effects of the ACE2/Ang-(1-7)/Mas axis on diabetes are not only limited to improving insulin sensitivity and glycemic control, but also involve the regulation of glucose metabolism in liver, muscle and adipose tissue. Recent studies have shown that activation of the ACE2/Ang-(1-7)/Mas axis significantly reduces the incidence of diabetes and the risk of complications by improving insulin resistance, enhancing β-cell function, and regulating endocrine and metabolic processes [52]. In addition, studies have revealed that Ang-(1-7) may exert anti-renal disease potential by reducing renal inflammation, fibrosis and improving renal microcirculation.

Nevertheless, targeting the ACE2/Ang-(1-7)/Mas axis in diabetes treatment still faces several challenges. First, although studies have revealed the critical role of this pathway in glucose metabolism, its specific mechanisms in postprandial glucose regulation, insulin secretion, and its role among different tissues are still not completely clear [54]. In addition, although some studies have demonstrated the beneficial effects of ACE2/Ang-(1-7)/Mas axis activation on diabetes-related complications, how to precisely regulate this pathway to ensure that its therapeutic efficacy is maximized and potential side effects are avoided remains a key to future research. Future studies should focus on elucidating the specific mechanisms of ACE2/Ang-(1-7)/Mas in diabetes and its

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complications, especially how to pharmacologically modulate this pathway to improve insulin resistance, β-cell function, and renal damage in diabetes. In addition, the development of drugs that can activate the ACE2/Ang-(1-7)/Mas axis or promote Ang-(1-7) production will provide novel clinical strategies for diabetes treatment. It is noteworthy that with the deepening of basic research, clinical trials and the development of new drugs, the ACE2/Ang-(1-7)/Mas axis may not only play an important role in diabetes treatment, but may provide innovative targets for intervention in the multiple complications caused by diabetes.

5. Conclusion

This paper delineates both composition mechanism underlying classical RAS systems revealing intricate associations between these systems metabolic regulatory factors such obesity autophagy Further investigations indicate abnormalities present within RAS closely correlate occurrence progression various metabolic disorders including diabetes Through clinical evidence it becomes apparent that utilization RAS inhibitors markedly improves insulin resistance showcasing distinct advantages over conventional therapies when mitigating complications arising from diabetes Given these favorable attributes numerous studies have explored combinatorial approaches integrating them alongside alternative antidiabetic medications yielding promising results affirming enhanced efficacy achieved through combination regimens Moving forward focus must shift towards thorough examination pertaining specifically how interactions involving ACE2 pathways affect liver glucose homeostasis postprandial glycemic control broader implications across diverse organ systems Concurrently efforts ought extend beyond solely diabetic contexts aiming reveal intricacies governing ATIR MAS receptors' involvement neurodegenerative phenomena ultimately uncovering viable target options available utilizing RA system inhibition strategies thus providing fresh perspectives methods tackling relevant health issues.

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