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Targeting the Renin-Angiotensin System in Obesity-Driven Hyperlipidemia and Hypertension

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ABSTRACT

The renin-angiotensin system (RAS) plays a crucial role in the regulation of blood pressure, fluid balance, and lipid metabolism. Dysregulation of the RAS has been implicated in the pathogenesis of obesity-driven hyperlipidemia and hypertension, two major components of metabolic syndrome that significantly increase the risk of cardiovascular disease. In obese individuals, increased adipose tissue promotes local activation of the RAS, leading to heightened angiotensin II (Ang II) activity, oxidative stress, inflammation, and impaired lipid metabolism. These pathological mechanisms contribute to both elevated blood pressure and abnormal lipid profiles. Targeting the RAS through angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and novel agents offers therapeutic potential in reducing obesity-associated hypertension and hyperlipidemia. This review discusses the molecular mechanisms linking obesity to RAS overactivation, examines current pharmacological strategies, and explores emerging therapeutic options aimed at modulating the RAS in the context of obesity-driven cardiometabolic disorders.

Keywords: Renin-angiotensin system, obesity, hyperlipidemia, hypertension, angiotensin II, ACE inhibitors, ARBs, metabolic syndrome, cardiovascular disease.

INTRODUCTION

Obesity is a global health crisis that affects millions worldwide, and its prevalence continues to rise at alarming rates. It is associated with a multitude of metabolic complications, among which hyperlipidemia (elevated levels of lipids in the blood) and hypertension (high blood pressure) are two of the most significant contributors to cardiovascular disease (CVD), the leading cause of death globally[1–3]. These conditions not only exacerbate the risk of heart attacks, strokes, and other cardiovascular events, but they also lead to the development of other chronic conditions such as type 2 diabetes, kidney disease, and atherosclerosis [4, 5]. One of the key mechanisms linking obesity to these metabolic disturbances is the dysregulation of the renin-angiotensin system (RAS) [6, 7]. The RAS plays a critical role in the regulation of blood pressure, electrolyte balance, and vascular resistance through a complex network of hormones, enzymes, and receptors[8–10]. Under normal physiological conditions, the RAS maintains homeostasis by controlling vasoconstriction and fluid retention. However, in obese individuals, the RAS becomes overactivated, leading to a host of detrimental effects [11].

The overactivation of the RAS in obesity is thought to occur through several mechanisms, including increased adipose tissue-derived factors, such as angiotensinogen, which is produced in excess by adipocytes[6]. This upregulation of angiotensinogen, the precursor to the potent vasoconstrictor angiotensin II, drives the pathological overactivity of the system. Angiotensin II plays a pivotal role in promoting vasoconstriction, increasing blood pressure, and causing inflammation and fibrosis within blood vessels. It also stimulates aldosterone secretion, which leads to sodium retention and further exacerbates hypertension [12]. Moreover, angiotensin II has been implicated in the development of hyperlipidemia by altering lipid metabolism. It induces oxidative stress and inflammation, leading to endothelial dysfunction, which impairs the normal lipid clearance mechanisms, contributing to the accumulation of cholesterol and triglycerides in the bloodstream[13]. This results in the formation of atherosclerotic plaques, which further increases the risk of cardiovascular events in obese individuals. The intricate interplay between RAS dysregulation, obesity, hyperlipidemia, and hypertension creates a vicious cycle where each condition exacerbates the others. The chronic low-grade inflammation associated with obesity further

aggravates this cycle, as inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) contribute to RAS overactivation and metabolic dysregulation [14].

Given the critical role of the RAS in the pathogenesis of obesity-related metabolic complications, targeting this system has become a promising therapeutic strategy. Traditional pharmacological approaches, such as angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs), have been widely used to treat hypertension and reduce cardiovascular risk in obese individuals. These agents block the effects of angiotensin II, thereby lowering blood pressure and reducing inflammation and oxidative stress. Emerging therapies targeting other components of the RAS, such as direct renin inhibitors or selective aldosterone receptor antagonists, offer additional avenues for intervention. Beyond pharmacological interventions, lifestyle modifications, including weight loss through diet and exercise, can attenuate RAS overactivity and improve metabolic outcomes in obese individuals. Recent research also suggests that targeting adipose tissue inflammation and improving insulin sensitivity may indirectly modulate RAS activity, offering new potential therapeutic targets.

This review aims to provide a comprehensive understanding of the complex relationship between obesity, RAS dysregulation, hyperlipidemia, and hypertension. By highlighting both current and emerging therapeutic strategies aimed at mitigating these metabolic disturbances, it underscores the importance of a multifaceted approach to addressing the global obesity epidemic and its associated health risks.

The RAS is a hormone-regulating system essential for maintaining blood pressure and fluid balance. Key components include renin, angiotensinogen, angiotensin I (Ang I), and angiotensin II (Ang II). Renin, released by the kidneys, cleaves angiotensinogen to form Ang I, which is then converted to Ang II by angiotensin-converting enzyme (ACE). Ang II acts primarily on angiotensin type 1 (AT1) receptors, inducing vasoconstriction, sodium retention, and aldosterone secretion[15]. These actions elevate blood pressure and enhance sodium and water reabsorption, but in obesity, excessive activation of the RAS can have deleterious consequences.

Obesity and Renin-Angiotensin System Over-activation

Obesity, characterized by an excess of adipose tissue, alters the physiological balance of the RAS. Adipocytes themselves are a source of angiotensinogen, promoting local RAS activation[16]. As adipose tissue expands, it triggers an increase in Ang II production and subsequent activation of AT1 receptors in various tissues, including the vasculature, kidneys, and liver. This promotes vasoconstriction, sodium retention, and inflammatory responses, leading to hypertension and altered lipid metabolism. Furthermore, obesity-associated insulin resistance exacerbates these processes, enhancing RAS activity and fueling a vicious cycle of metabolic dysfunction[17].

RAS and Hyperlipidemia in Obesity

Hyperlipidemia in obesity is characterized by elevated levels of circulating triglycerides, low-density lipoprotein (LDL) cholesterol, and reduced high-density lipoprotein (HDL) cholesterol[18]. Dyslipidemia contributes to the development of atherosclerosis, a major cardiovascular risk. Ang II has been shown to promote the uptake of LDL cholesterol into vascular walls, enhancing atherogenesis. In addition, Ang II-induced oxidative stress and inflammation impair lipid metabolism, contributing to abnormal lipid profiles in obese individuals[19]. Thus, RAS overactivation not only drives hypertension but also plays a significant role in obesity-related hyperlipidemia.

TARGETING THE RENIN-ANGIOTENSIN SYSTEM: PHARMACOLOGICAL APPROACHES

Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)

ACE inhibitors, such as enalapril and lisinopril, are widely used in the treatment of hypertension. By blocking the conversion of Ang I to Ang II, ACE inhibitors reduce vasoconstriction and lower blood pressure[20]. In obese individuals, ACE inhibitors have been shown to improve both blood pressure control and lipid profiles by reducing oxidative stress and inflammation. Moreover, ACE inhibitors can enhance insulin sensitivity, further mitigating the metabolic disturbances seen in obesity[20].

Angiotensin II Receptor Blockers (ARBs)

ARBs, including losartan and valsartan, selectively block AT1 receptors, preventing Ang II from exerting its vasoconstrictive and pro-inflammatory effects.[21] ARBs are effective in lowering blood pressure in obese patients, with some studies demonstrating their beneficial effects on lipid metabolism. ARBs also exhibit antioxidant properties, which may contribute to the attenuation of RAS-mediated oxidative stress and its associated dyslipidemia [21].

Novel Agents Targeting the RAS

Emerging therapeutic agents that target specific components of the RAS hold promise for more

precise management of obesity-driven metabolic disorders. Aliskiren, a direct renin inhibitor, reduces Ang I and Ang II production, providing a more upstream blockade of the RAS[22]. Experimental drugs targeting alternative pathways, such as the angiotensin-converting enzyme 2 (ACE2)/angiotensin-(1-7) axis, are also being explored for their potential to counteract the adverse effects of Ang II in obesity. These agents could offer novel strategies for tackling the dual challenge of hyperlipidemia and hypertension in obese individuals[22].

RAS Blockade Beyond Blood Pressure Control: Impacts on Lipid Metabolism

RAS inhibition has broader metabolic benefits beyond blood pressure regulation. ACE inhibitors and ARBs have been shown to reduce triglyceride levels and improve cholesterol profiles in clinical studies [23]. By mitigating Ang II-induced lipid peroxidation and inflammatory responses, RAS blockade can reverse some of the key drivers of hyperlipidemia in obesity. These findings underscore the potential of RAS-targeted therapies to provide comprehensive cardiovascular protection in obese patients.

Challenges and Future Directions

While RAS-targeting therapies are effective in managing obesity-driven hypertension and hyperlipidemia, challenges remain. Obesity-related RAS dysregulation is complex, involving both systemic and local (adipose tissue) activation. Future research should focus on understanding these mechanisms in greater detail to develop more targeted therapies. Additionally, combining RAS inhibitors with lifestyle interventions, such as weight loss and exercise, may enhance their therapeutic efficacy. Investigating the potential synergistic effects of RAS blockade with other metabolic pathways, including insulin signaling and lipid metabolism, could also yield new treatment strategies.

CONCLUSION

The renin-angiotensin system plays a central role in the pathophysiology of obesity-driven hypertension and hyperlipidemia. Overactivation of the RAS in obese individuals leads to elevated Ang II levels, oxidative stress, and inflammation, all of which contribute to cardiovascular risk. Pharmacological targeting of the RAS using ACE inhibitors, ARBs, and novel agents offers a promising approach to mitigating these metabolic disturbances. However, continued research is needed to refine these therapies and explore new strategies for managing the complex interplay between obesity, lipid metabolism, and hypertension.

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