MECHANISMS OF ENDOTHELIAL DYSFUNCTION IN RENAL VESSELS INDUCED BY ELEVATED URIC ACID LEVELS

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Abstract: Elevated uric acid is a significant contributor to endothelial dysfunction in renal vessels. High uric acid levels increase oxidative stress, reduce nitric oxide availability, and activate pro-inflammatory pathways, leading to impaired renal perfusion, glomerular injury, and hypertension. Understanding these mechanisms is essential for developing targeted interventions to prevent or mitigate renal and cardiovascular complications associated with hyperuricemia. This study reviews recent findings on molecular pathways and clinical implications of uric acid-induced endothelial dysfunction in renal vasculature.

Keywords: Uric acid, Endothelial dysfunction, Renal vessels, Oxidative stress, Nitric oxide, Inflammation, Hyperuricemia

INTRODUCTION

The endothelium is a critical layer lining the inner surface of blood vessels, responsible for regulating vascular tone, blood flow, and various biochemical processes, including coagulation, inflammation, and oxidative balance. When endothelial function is impaired, a condition known as endothelial dysfunction occurs, contributing to the development of multiple diseases such as hypertension, atherosclerosis, and kidney disorders. Recent research highlights elevated uric acid levels as an important factor in the pathogenesis of endothelial dysfunction. Uric acid, a product of purine metabolism, can accumulate excessively, causing hyperuricemia. High uric acid levels affect endothelial cells not only in crystal form, as in gout, but also in soluble form by increasing oxidative stress, reducing nitric oxide production, and activating pro-inflammatory pathways. These processes lead to structural and functional alterations in renal vasculature, impair glomerular filtration, and may promote renal hypertension. Moreover, uric acid influences intracellular signaling pathways, further mediating

endothelial dysfunction at the molecular level. This study aims to examine the mechanisms through which elevated uric acid induces endothelial dysfunction in renal vessels, focusing on molecular pathways and potential clinical consequences.

Main part

Elevated uric acid levels directly affect glomerular and peritubular capillaries, exerting both structural and functional toxicity. Soluble uric acid promotes oxidative stress within endothelial cells, impairing the production of nitric oxide (NO), a key vasodilator. Simultaneously, uric acid enhances the release of vasoconstrictor mediators such as endothelin-1, leading to increased vascular resistance and reduced renal perfusion. At the cellular level, uric acid activates intracellular signaling pathways, including mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB), which induce pro-inflammatory gene expression. This contributes to leukocyte adhesion and low-grade vascular inflammation. In addition, elevated uric acid can impair mitochondrial function, promoting reactive oxygen species (ROS) generation and endothelial apoptosis. Clinically, these changes are associated with glomerular injury, tubulointerstitial fibrosis, and the development of hypertension. The imbalance between vasodilatory and vasoconstrictive factors results in persistent microvascular dysfunction. Overall, hyperuricemia creates a pro-oxidative, pro-inflammatory, and pro-apoptotic environment in renal endothelial cells, establishing the foundation for progressive renal damage and cardiovascular complications.

Endothelial dysfunction induced by uric acid is mediated by several molecular signaling pathways. Activation of MAPK and NF-κB pathways increases the transcription of pro-inflammatory cytokines and adhesion molecules, including interleukin-1β, tumor necrosis factor-alpha (TNF-α), vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1). These changes promote leukocyte recruitment and sustained vascular inflammation. At the same time, uric acid inhibits the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway, reducing endothelial nitric oxide synthase (eNOS) activity and NO production. Reduced NO bioavailability compromises vasodilation and antithrombotic functions. Excess ROS production caused by uric acid further damages cell membranes, lipids, and proteins, leading to oxidative stress. Inflammasome activation, particularly NLRP3, amplifies cytokine release and endothelial injury. Collectively, these mechanisms establish a feedback loop, where inflammation, oxidative stress, and impaired NO signaling perpetuate endothelial dysfunction. Understanding these molecular processes is essential for developing targeted therapies to prevent or reverse renal vascular damage associated with hyperuricemia.

Endothelial dysfunction in renal vessels due to elevated uric acid manifests clinically as increased vascular resistance, reduced glomerular filtration, and renal hypertension. These changes contribute to the progression of chronic kidney disease and are often associated with cardiovascular comorbidities. Therapeutic strategies focus on lowering uric acid levels using agents such as allopurinol or febuxostat, which can reduce oxidative stress and improve endothelial function. Antihypertensive medications, particularly those that enhance NO bioavailability, are also beneficial in restoring vascular homeostasis. Additionally, anti-inflammatory and antioxidant interventions may help mitigate endothelial injury. Monitoring biomarkers of endothelial dysfunction, oxidative stress, and uric acid levels allows for personalized treatment planning. Future research should aim to clarify the complex interaction between uric acid, intracellular signaling pathways, and renal vascular pathology, thereby facilitating the development of novel pharmacological approaches. Overall, early recognition and management of hyperuricemia are critical in preventing progressive renal damage and improving patient outcomes.

Conclusion

Elevated uric acid contributes significantly to endothelial dysfunction in renal vessels. It promotes oxidative stress, reduces nitric oxide availability, and activates inflammatory pathways, leading to impaired renal blood flow and vascular damage. These changes increase the risk of hypertension and chronic kidney disease. Controlling uric acid levels and supporting endothelial function are essential to prevent renal and cardiovascular complications. Early intervention may improve vascular health and reduce disease progression.

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