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Importance of Angiotensinogen as an Upstream Factor of the Intrarenal Renin - Angiotensin System in Patients with Diabetic Nephropathy

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Abstract

The renin-angiotensin system has been found to be a critical regulator of blood volume and systemic vascular resistance. Additionally, the intrarenal renin-angiotensin system is important in the development and progression of diabetic nephropathy. Research on angiotensinogen as a precursor of angiotensin and an upstream factor of the renin–angiotensin system has shown that urinary angiotensinogen is useful as an early biomarker of diabetic nephropathy. However, the mechanisms underlying the increased expression and secretion of angiotensinogen in patients with diabetic nephropathy remains unclear. The present mini-review focuses on the importance of angiotensinogen in diabetic nephropathy.

Introduction

Diabetes mellitus is associated with an increased incidence of structural and functional derangements is the kidney, eventually leading to end-stage renal disease in a significant fraction of afflicted individuals [1]. This mini-review explains the role of the intrarenal renin–angiotensin system in the mechanism of diabetic nephropathy. Interest has recently increased in both the local and organized renin–angiotensin system. We herein overview the whole system.

Our interest lies is the mechanisms underlying the increased expression and secretion of angiotensinogen in patients with diabetic nephropathy, especially whether the expression of angiotensinogen increases in the development of diabetic nephropathy. In patients with hypertensive diabetic nephropathy who receive angiotensin II receptor blockers, the urinary levels of angiotensinogen and the blood pressure are decreased. This suggests that the renoprotective effect of angiotensin II receptor blockers may involve suppression of the intrarenal angiotensinogen level in patients with type 2 diabetes [2]. Furthermore, the increase in the urinary angiotensinogen level was greater in normoalbuminuric patients with type 1 diabetes than in control subjects, although an increased plasma angiotensinogen level was not observed [3]. We investigated the expression and secretion of angiotensinogen using a mouse model of type 1 diabetes and expected to find increased secretion prior to the onset of urinary albumin. Our hypothesis was that regulation of the angiotensinogen level will expect the preventive effects of diabetic nephropathy.

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Renin-angiotensin system

The renin-angiotensin system contributes to blood pressure as well as fluid and electrolyte homeostasis [4]. Angiotensinogen is the substrate for the peptides angiotensin II and angiotensin-(1-7). The formation of angiotensin II is dependent upon the availability of angiotensinogen and angiotensin I as well as the activities of renin, angiotensin-converting enzyme, angiotensin-converting enzyme 2, and components of angiotensin-converting enzyme-dependent enzymatic pathways such as serine proteases. Angiotensin-(1-7) can be formed directly from angiotensin II through hydrolysis of angiotensin-converting enzyme 2 or indirectly from angiotensin I via an intermediate step of the formation of angiotensin-(1-9) through hydrolysis of angiotensin-converting enzyme 2 and angiotensin-converting enzyme. The actions of angiotensin II are determined by signaling via angiotensin II type 1 and type 2 receptors [5] and putative angiotensin-(1-7) receptor [6].

Intrarenal renin-angiotensin system in diabetic nephropathy

Attention to the local renin–angiotensin system [7] in the brain [8], heart [9], kidney [5,10], vasculature [11,12], and adrenal glands [13] has recently increased. The renal renin-angiotensin system has been found to be particularly important because all components necessary to generate intrarenal angiotensin II are included in the nephron.

Angiotensinogen is the only known substrate for renin, which is the rate-limiting enzyme of the renin-angiotensin system. Because the concentration of angiotensinogen is close to the Michaelis-Menten constant for renin, both the renin level and angiotensinogen level are thought to affect the formation rate of angiotensin peptides [14]. The angiotensinogen gene is specifically present in the proximal tubules [15]. Angiotensinogen mRNA is expressed largely in the proximal convoluted tubules and proximal straight tubules; only small amounts are expressed in the glomeruli and vasa recta as revealed by reverse transcription and polymerase chain reaction [16]. In addition, renal angiotensinogen protein is specifically located in the proximal convoluted tubules as shown by immunohistochemistry [17]. Immunostaining for angiotensinogen protein is strongly positive in the proximal convoluted tubules and proximal straight tubules and weakly positive in the glomeruli and vasa recta; however, there is no perceptible staining in the distal tubules or collecting ducts [18].

Urinary albumin is commonly used as a marker of diabetic nephropathy in the clinical setting. Diabetic nephropathy has been thought to progress unidirectionally from microalbuminuria to end-stage renal failure. However, recent findings indicate that many patients who have been diagnosed with diabetic nephropathy recover normal albuminuria. Furthermore, one-third of patients with diabetic nephropathy lose renal function because of microalbuminuria. Therefore, a highly sensitive and specific marker of activation of diabetic nephropathy is necessary [1].

Using mice with streptozotocin-induced diabetes (mouse model of type 1 diabetes), we investigated the increase in urinary albumin excretion and angiotensinogen excretion over time in the development of diabetic nephropathy [19]. Our results showed that increased urinary angiotensinogen excretion was present prior to the onset of urinary albumin in mice with streptozotocin-induced type 1 diabetes. At that time, the expression of angiotensinogen in the kidneys, especially in the proximal tubules, was increased. This finding suggests that urinary angiotensinogen might be useful as an early biomarker of activation of the renin-angiotensin system in diabetic nephropathy.

Further studies

Terami et al. [20] and Satiropoj et al. [21] confirmed urinary angiotensinogen as an early biomarker of activation of the renin–angiotensin system in diabetes. Additionally, cellular experiments have shown that high glucose and oxidative stress increase angiotensinogen [22,23]. Recent studies have revealed that angiotensin II receptor blockers suppress the activation of the local renin–angiotensin system [2]. However, few reports have focused on the relationship between the renin–angiotensin system and food components. Further research on the mechanism underlying the increase in angiotensinogen and the development of preventive medicine is expected.

Conclusion

We have shown that the expression and secretion of angiotensinogen is increased in the development of diabetic nephropathy. Research into angiotensinogen expression and secretion of the status of the intrarenal renin–angiotensin system may be of substantial clinical importance. It may be particularly helpful in determining the efficacy of treatment to reduce intrarenal angiotensin II levels.

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