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Review

The Role of Renin Angiotensin Aldosterone System Genes in Diabetic Nephropathy

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ABSTRACT

The role of the renin angiotensin aldosterone system (RAAS) and the gene variants of its components in susceptibility to diabetic nephropathy (DN) have been investigated in numerous studies. The effects of some RAAS gene variants, including angiotensin converting enzyme (ACE), angiotensinogen (AGT) and angiotensin II type 1 receptor (AT1R), on the risk for DN have been studied more extensively, but there has been controversy. The reasons for controversy in this field could be attributed to the effect of ethnicity, gender, stage of diabetes complications, the presence of intrarenal RAAS, methodologic limitations of the association studies in multifactorial diseases, inadequate sample size, genetic heterogeneity, and the lack of studies that involved all RAAS genes and their interactions. This review looks at the current available information about the role of all RAAS gene variants in the pathogenesis of DN. Further, the concomitant study of both systemic and local RAAS, counter-regulators of ACE and ACE2, and also AT1R and angiotensin II type 2 receptor (AT2R) genes could help to elucidate the role of the genes of this system in the pathogenesis of DN.

Mots clés :
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rénine

RÉSUMÉ

De nombreuses études ont examiné le rôle du système rénine-angiotensine-aldostérone (SRAA) et les variants génétiques de ses composantes dans la susceptibilité à la néphropathie diabétique (ND). Les effets de certains variants génétiques du SRAA, dont l'enzyme de conversion de l'angiotensine (ECA), l'angiotensinogène (AGT) et le récepteur de type 1 de l'angiotensine II (AT1R) sur le risque de ND ont fait l'objet d'études plus approfondies, mais controversées. Les raisons de cette controverse seraient attribuées à l'effet de l'ethnicité, du genre, du stade des complications liées au diabète, de la présence du SRAA intrarénal, des limites méthodologiques des études d'association entre les maladies multifactorielles, de la taille inadéquate de l'échantillon, de l'hétérogénéité génétique et du manque d'études liées aux gènes du SRAA et de leurs interactions. Cette revue analyse les informations actuellement disponibles sur le rôle de tous les variants génétiques du SRAA dans la pathogenèse de la ND. De plus, l'étude concomitante du SRAA tant sur le plan systémique que local, la contre-régulation de l'ECA et de l'enzyme de conversion de l'angiotensine II (ECA2), ainsi que les gènes de l'AT1R et le récepteur de type 2 de l'angiotensine II de type 2 (AT2R) pourraient contribuer à l'élucidation du rôle des gènes de ce système dans la pathogenèse de la ND.

Introduction

Diabetes mellitus is the main problem of public health and is a significant economic burden worldwide. Patients who have diabetes are susceptible to developing microvascular complications (nephropathy, retinopathy and neuropathy) (1). The absence of diabetes micro- and macrovascular complications in some patients in spite of poor glycemic control and ethnically dependent susceptibility to diabetic nephropathy (DN) suggest the role of genetics in the causes of diabetes (2). The genes of the renin angiotensin aldosterone system (RAAS) play important roles in glucose metabolism and the regulation of blood pressure, electrolytes and fluid homeostasis. The RAAS genes consist of renin, angiotensinogen (AGT), angiotensin converting enzyme (ACE), angiotensin converting enzyme 2 (ACE2), angiotensin II type 1 receptor (AT1R) and angiotensin II type 2 receptor (AT2R) (3). The enzymatic cascade of production of 2 counter peptides of angiotensin II (Ang II) and Ang (1-7) in the RAAS are demonstrated in the Figure 1. All components of the systemic RAAS are present in the local or tissue RAAS, which

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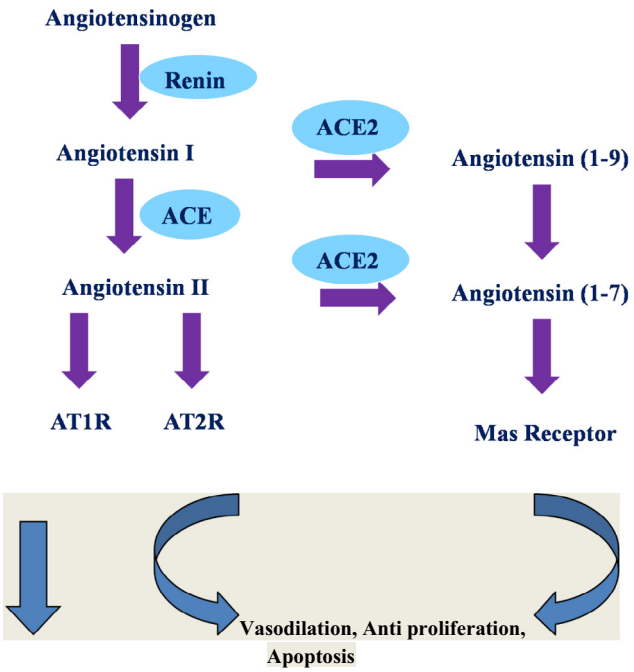

Figure 1. The pathways involved in the formation and action of angiotensin II and angiotensin (1-7). The angiotensinogen is cleaved to decapeptide of angiotensin I by renin. Angiotensin I is degraded to angiotensin II, an active octapeptide, by the ACE. Angiotensin II is recognized by AT1R and AT2R. Angiotensin (1-7), which is produced by the action of ACE2 on the angiotensin II, antagonizes the actions of angiotensin II/AT1R through binding to the Mas receptor. *ACE,* angiotensin converting enzyme; *AT1R,* angiotensin type 1 receptor; *AT2R,* angiotensin type 2 receptor.

is regulated independent of the systemic RAAS and is found in kidneys, heart, blood vessels and many other tissues (4).

Knowledge of the functional role of the RAAS gene variants in susceptibility to DN will help to develop personalized medicine in the management of this complication. The present review discusses the role of RAAS gene variants in the pathogenesis of DN.

Diabetic Nephropathy

DN is a serious microvascular complication of diabetes and is the leading cause of end stage renal disease (ESRD) (5). DN develops in 30% to 35% of patients with both type 1 and type 2 diabetes mellitus, irrespective of blood glucose control (6). The pathogenesis of DN development is multifactorial; it involves genetic factors and metabolic (poor glycemic control and hyperlipidemia) and systemic and renal hemodynamic factors. In DN, both the systemic and renal RAAS are hyperactive (4) and have important roles in its pathogenesis (3). DN is manifested by microalbuminuria that subsequently can progress to macroalbuminuria (7).

Renin and prorenin genes and DN

The renin gene locates on chromosome 1q32 and encodes the inactive precursor of prorenin and also expresses renin. Renin is an aspartyl protease that catalyses the rate-limiting reaction of cleavage AGT into Ang I (8). In patients with DN, the levels of prorenin, renin, ACE and Ang II are increased (9).

The role of the renin gene variants in the pathogenesis of DN has been addressed in limited studies. A weak association between the renin gene polymorphism with the risk for developing DN in patients with type 1 diabetes has been suggested, and only 1 of the studied polymorphisms (BglI B/b) of the renin gene was associated with the risk for DN (10). However, the renin C-4063T polymorphism was not associated with the risk for DN (11).

A receptor designates (pro) renin receptor (P) RR to bind equally to renin and prorenin with high affinity. The gene of (P) RR is located on the X chromosome in the locus p11.4 (12). A role for (P) RR in the regulation of blood pressure has been reported by the Japanese cohort study of Ohasama, which suggested the T allele of IVS5+169 C:T (rs5918007) was associated with ambulatory blood pressure in men (13). Similarly, the role of the IVS5+169 C:T polymorphism in blood pressure regulation in Caucasian men was confirmed later. The study demonstrated a higher serum level of aldosterone and systolic blood pressure in the presence of the T allele compared to the C allele (14).

AGT gene and DN

The level of AGT is the limiting factor for Ang II production, and increased AGT concentration elevates Ang II (15). The most studied polymorphism of AGT M235T locates on chromosome 1q41-q45 (rs699) and encodes threonine instead of methionine. The presence of the AGT 235T allele is associated with increased plasma levels of AGT and higher susceptibility to cardiovascular and renal diseases and essential hypertension (16). There are controversial reports related to the role of AGT M235T in susceptibility to DN (Table 1).

AGT M235T in patients with type 1 diabetes and DN

The absence of a role for the AGT M235T polymorphism in the pathogenesis of DN in type 1 diabetes has been suggested (9,16,17). In contrast, an association between the AGT M235T polymorphism and the development of persistent microalbuminuria in children (18) and in those with higher urinary albumin excretion and DN has been reported (19).

AGT M235T in patients with type 2 diabetes and DN

A lack of association between AGT M235T and susceptibility to DN among Caucasians, Turkish and Mexican American families and in a recent meta-analysis has been reported (20-25,26), and that might be due to the influence of this polymorphism on the approximately 5% variability in AGT level (27). However, in a subsequent study of Turkish patients with type 2 diabetes (28) and also in Tunisians, the AGT 235T allele was associated with the risk for DN (11). Further, association of the AGT TT genotype with susceptibility and faster progression to ESRD in patients with both type 1 and type 2 diabetes has been demonstrated (29,30).

ACE

The ACE, by generating the vasoconstrictor peptide of Ang II and the inactivation of vasodilators of Ang (1-7) and bradykinine, is known as a prohypertensive enzyme (31).

The ACE gene, located on chromosome 17q23, comprises 26 exons (32). The presence or absence of a 287 base pairs insert in intron 16 of the ACE gene designated as ACE insertion/deletion (I/D) polymorphism (rs1799752) is the most studied variant of the ACE gene (33). The physiologic importance of this polymorphism is the association of the D allele with the highest systemic and renal ACE activity, which results in increased glomerular filtration rates (7).