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Renalase, a new secretory enzyme: Its role in hypertensive-ischemic cardiovascular diseases

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Renalase, a novel amine oxidase, is mainly expressed in the kidney, heart, and skeletal muscle. It has been known to degrade circulating catecholamines and plays a crucial role in human diseases. Recent studies have demonstrated its structure, unique bioactivities, function, and the gene polymorphisms in human diseases. In this review, we summarize the effects of renalase on hypertension, myocardial ischemia, acute kidney injury (AKI), ischemic stroke, cardiac dysfunction, organ transplantation, and diabetes mellitus reported in numerous studies.

Keywords: Renalase • Hypertension • Ischemia • Cardiac Dysfunction • Organ Transplantation • Diabetes Mellitus

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Background

In 2005, researchers at Yale University analyzed all the genes of targeted proteins published by the Mammalian Gene Collection Project (MGC). They found 1 gene, named Renalase, was robustly expressed in the kidney. Moreover, they identified that the renalase gene has 9 exons spanning approximately 3.11×10{5bp, resides on chromosome 10 at q23.33, and encodes a protein with 342 AAs with a molecular mass of 37.8 kDa [1].

Human renalase (hRenalase) mRNA include 4 splice variants (renalase 1–4). Renalase1 is very well conserved. Its structure has a signal peptide at the N-terminus (AAs1-17), a FAD-binding site (AAs4–35), and an amine oxidase domain (AAs75–339). Some investigators speculate that hRenalase 3 and 4 have no amine oxidase function, because their structure has shortened amine oxidase domains. The crystal structure of hRenalase1 indicates that it is a member of the flavoprotein superfamily. It has 13.2% AA identity with monoamine oxidase A (MAO-A). However, renalase is not a monoamine oxidase; it effectively metabolizes the circulating catecholamines in a different way from those seen in MAO that resides on the external membrane of mitochondria and degrades intracellular catecholamines [2–5].

Renalase, using NAD(P)H as a cofactor, degrades circulating catecholamines (epinephrine >L-DOPA >dopamine = norepinephrine, NE). An immunohistochemistry study revealed that Renalase can be detected in kidney, heart, skeletal muscle, small intestine, brain, and peripheral nervous system. Therefore, researchers conclude that Renalase is significantly associated with human diseases [6–9].

Renalase and Hypertension

Hypertension is a common cardiovascular disease, which arises from the action of multiple genetic and environmental factors. The activation of the sympathetic nervous system is one of these mechanisms. Catecholamines, such as epinephrine, norepinephrine, and dopamine, are involved in sympathetic activation. The elevation of these substances can directly lead to hypertension. Renalase indirectly regulates cardiac function and blood pressure by degrading catecholamines [10].

We was previously reported that renal denervation can lower blood pressure, perhaps due to the suppression of sympathetic nerves, the increase in plasma renalase level, and renalase expression in the kidney [11]. After Sprague-Dawley (SD) rats were injected with exogenous recombinant renalase, their systolic pressure, diastolic pressure, and mean arterial pressure mildly or moderately decreased [1]. The other authors had demonstrated that renalase regulated blood pressure; they used RNAi to inhibit the renalase gene expression, and when the decrease of renalase gene expression reached 40%, the blood pressure increased by 13 mmHg [12]. In addition, the intrarenal dopaminergic system also plays a critical role in regulating blood pressure. One study team reported that animals fed a high-phosphate diet had a significant increase in the activity of renal DOPA (l-dihydroxyphenylalanine) decarboxylase and significant reductions in renalase. Their results indicated that the action of renalase may be attributed to the regulation of the intrarenal dopaminergic system [13]. Another study found that renalase expression is modulated by salt intake, and recombinant renalase has a hypotensive effect on blood pressure in Dahl salt-sensitive rats [14].

To further confirm the association between the renalase and hypertension, a study recruited 1317 hypertensive patients and 1269 normotensive controls in a northern Han Chinese population, reporting that essential hypertension was highly associated with rs2576178 GG genotype and rs2296545 CC genotype [15]. Another study investigated the genotype of rs2576178 polymorphism in 369 patients and rs10887800 polymorphism in 421 dialyzed patients, and they found an association between renalase gene polymorphisms and hypertension in dialyzed patients [16]. According to these studies, we hypothesized that renalase regulates blood pressure by down-regulating sympathetic nervous system activity, or by degrading renal dopamine (which has both natriuretic and phosphaturic properties). These findings may provide novel genetic viewpoints and provide insight into the pathophysiology of hypertension.

Despite recent substantial advances in the treatment of hypertension, blood pressure in most patients still remains suboptimally controlled. Therefore, the need for innovative strategies to lower blood pressure (BP) is emerging. The new therapeutic prospect of hypertension has arisen due to the unique function of renalase, which regulates blood pressure. Its discovery might provide a novel pathophysiological link between sympathetic tone and BP [17].

Renalase and Ischemic-Related Diseases (Myocardial Ischemia, AKI, and Ischemic Stroke)

Renalase can be detected in kidney, heart, and brain. Numerous *in vitro* experiments in animals have confirmed that renalase protects against ischemic myocardial damage, AKI, and ischemic stroke.

One study reported that a renalase gene knockout mouse model demonstrated higher plasma catecholamines level and blood pressure than in the control group. Although plasma

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aldosterone level, kidney function, and cardiac systolic function did not change, renalase gene knock-out model mice poorly tolerated cardiac ischemia and easily developed myocardial necrosis and apoptosis. Treatment with exogenous recombinant renalase completely reduced the myocardial damage [18]. This finding indicates that renalase can reduce cell damage caused by ischemia, improve cell tolerance to ischemia and reduce myocardial cell apoptosis. Another study genotyped the rs2296545 SNP (Glu37Asp) in 590 Caucasian subjects and demonstrated that the CC genotype had increased risk of inducible ischemia (OR=1.49, 95% CI 0.99–2.24). The functional missense polymorphism in renalase (Glu37Asp) is associated with ischemia in persons with stable coronary artery disease [19].

Animal experimental study has demonstrated that circulating renalase was remarkably low after renal ischemia-reperfusion injury, while plasma catecholamine level increased significantly. Moreover, renal tubular inflammation, necrosis, and apoptosis were more severe, and catecholamine levels were higher in a renalase deficiency model. Exogenous recombinant renalase can decrease catecholamine level and protect against ischemic AKI [20].

Current studies indicated that renalase is strongly associated with hypertension and ischemic diseases. Moreover, renalase may play a crucial role in ischemic stroke. To investigate the genetic association between renalase and ischemic stroke, a study group [21] genotyped single-nucleotide polymorphisms of the renalase gene in 507 ischemic stroke patients and 503 sex-matched controls from a northern Chinese Han population and found that rs10887800 and rs2576178 were significantly associated with ischemic stroke with hypertension by logistic regression (p=0.041 and p=0.038, respectively). Another study suggested that renalase might be associated with stroke in hemodialyzed patients, probably due to sympathetic nervous system hyperactivity [22]. It also means that renalase may be involved in ischemic stroke pathophysiology.

Taken together, these data suggest that renalase protects against ischemic injury by some undefined mechanism, and that circulating renalase might be a new biomarker for ischemic diseases. Furthermore, recombinant renalase may be useful in the prevention and treatment of ischemic diseases. Our study team hypothesized that renalase may protect against ischemic diseases by reducing cell necrosis, apoptosis, and local inflammatory reactions.

Renalase and Cardiac Dysfunction

During cardiac dysfunction, sympathetic nervous system (SNS) activity and levels of catecholamines were found to be increased as a compensatory attempt to augment the cardiac function, and this change had been associated with the prognosis of patients [23,24].

To verify the relationship between renalase and circulating NE in heart failure, investigators used an infarction-induced heart failure rat model. The results of their study indicated that the reduced renal blood flow that occurs in heart failure result in down-regulation of the synthesis of renalase and consequently caused increased circulating NE [25]. In another study, newborn male SD rats were treated with 5/6 nephrectomy to cause cardiac hypertrophy. The authors showed that up-regulation of cardiac G-protein-coupled receptor kinase-2 (GRK2) and NE could contribute to cardiac hypertrophy in nephrectomy rats. Moreover, compared to the preoperative level, the level of renalase obviously decreased postoperatively [26].

The association between renalase and cardiac dysfunction has been shown in animal experiments as well as in several human studies. Researchers compared 590 participants who had different genotypes, and found that the CC genotype had increased risk for developing left ventricular hypertrophy (OR=1.43, 95% CI 0.99–2.06), systolic dysfunction (OR=1.72, 95% CI 1.01–2.94), diastolic dysfunction (OR=1.75, 95% CI 1.05–2.93), and poor exercise capacity (OR=1.61, 95% CI 1.05–2.47), indicating that a functional missense polymorphism in renalase (Glu37Asp) is associated with cardiac dysfunction [19]. In addition, an *in vitro* heart perfusion study showed that exogenous recombinant renalase improved left ventricular function and reduced left ventricular pressure by means of an *in vitro* heart perfusion experiment [27].

These findings suggest that renalase may participate in the pathophysiological mechanism of cardiac dysfunction by down-regulating the activity of sympathetic nervous system (SNS) and degrading the level of catecholamines. However, on one hand a deeper and more accurate link between renalase and cardiac dysfunction need to be further researched, on the other hand whether or not renalase protein could be a new drug to improve the cardiac dysfunction should also need to be considered.

Renalase and Organ Transplantation

Beyond its association with the renal, cardiac disease, some investigations have recently demonstrated that renalase may play an important role in the pathogenesis of hypertension after organ transplantation and may affect the prognosis of the procedure.

Some studies had found that plasma renalase of hypertensive allograft recipients was significantly higher than in

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normotensives recipients, and renalase level could be predicted by renal function. In kidney transplant recipients, renalase correlated with age (r=0.29; P<.05), time after transplantation (r=0.34; P<.01), systolic blood pressure (r=0.28; P<.05), diastolic blood pressure (r=0.27; P<.05), serum creatinine (r=0.49; P<.001) [28–30]. In another study, renalase was significantly dependent on kidney function, which deteriorated with time after heart transplantation among 130 heart transplant recipients [31].

These findings demonstrate that renalase has a role in hypertension and renal function after transplantation. However, further studies are needed to explore possible novel targeted therapies in organ transplantation.

Renalase and Diabetes Mellitus (DM)

Diabetes mellitus, a common and complex disease, arises from multiple genetic and environmental factors. Renalase is also expressed in insulin-secreting cells [32]. One study analyzed 892 patients and 400 controls genotyped with 3 SNPs (rs2296545, rs2576178, and rs10887800) in the renalase gene, and reported that renalase gene polymorphisms are associated with hypertension in type 2 diabetes patients, and the G allele of this polymorphism might be useful in identifying diabetes patients at increased risk of stroke [33]. In addition, using a genome-wide association study (GWAS) in patients with type 1 diabetes, researchers have found 18 gene single-nucleotide polymorphisms that were associated with type 1 diabetes, one of which is renalase. Another study further confirmed that rs10509540 (renalase gene), which is located on chromosome 10q23.31, was strongly associated with type 1 diabetes [34,35].

The evidence from recent research suggests that the renalase gene may correlate with DM, but the mechanism involved remains unclear. Further studies are needed to evaluate the function of renalase in DM.

Conclusions

Renalase, a recently discovered amine oxidase, degrades circulating catecholamines and affects activity of the sympathetic nervous system and the intrarenal dopaminergic system. Mounting evidence from numerous studies demonstrates the capability of renalase recombinant proteins in lowing blood pressure as well as protecting myocardial cells from necrosis and apoptosis. The exact mechanism by which renalase regulates blood pressure and improves cardiac function is still unclear. However, renalase may be a potential drug or a novel therapeutic target for the prevention and treatment of hypertensive-ischemic cardiovascular diseases.

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