Corin, atrial natriuretic peptide and hypertension

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Keywords: blood pressure; genetic variants; natriuretic peptides; protease

Introduction

Maintaining a normal blood pressure is essential for a healthy life but apparently this is not an easy task to accomplish. Nearly 30% of adults worldwide develop hypertension [1], a disease that increases the risk of stroke, myocardial infarction and renal failure. The underlying cause of hypertension is complex and may involve many factors including blood volume, vascular response, neurohormonal regulation and genetic variations. Fundamentally, however, the disease reflects the failure of the body to adequately regulate salt and body fluid balance [2,3].

Consistently, most genetic mutations or variants associated with hypertension have been found in the genes involved in salt handling such as epithelial sodium channels, sodium/potassium transporters and proteins the renin–angiotensin–aldosterone system [4,5]. Additional genetic mutations or variants are found in the genes that may regulate kidney function such as α-adducin and endothelin 2 [4,5]. To date, however, the disease reflects the failure of the body to adequately regulate salt and body fluid balance.

Atrial natriuretic peptide in hypertension

Like the kidney, the heart plays an important role in regulating salt and water balance [6–8]. This function is mediated mainly by a cardiac hormone, atrial natriuretic peptide or factor (ANP or ANF). When blood sodium levels and pressure are increased, ANP is secreted from the heart. It binds to its receptor in the kidney and blood vessels, and promotes salt excretion, lowers blood volume and relaxes the vessel. This endocrine mechanism links the heart and kidney in maintaining a fine balance of electrolytes and body fluid.

The physiological importance of the ANP pathway has been shown in many animal studies. In mice, for example, ANP deficiency causes hypertension [9], whereas ANP overexpression results in hypotension [10]. The hypertension in ANP null mice is sensitive to high dietary salts, indicating that ANP is critical in regulating the response to salt in vivo. The heart also makes another peptide, brain or B-type natriuretic peptide (BNP), which has similar natriuretic and diuretic activity to that of ANP. BNP null mice, however, had normal blood pressure but developed cardiac fibrosis [11], suggesting that the physiological function of BNP may differ from that of ANP.

In humans, several single nucleotide polymorphisms (SNPs) have been found in the ANP gene. One of them (-C664G) is located in the promoter region. Genetic studies showed that the -664G allele was associated with low plasma ANP levels, high blood pressure and left ventricular hypertrophy in patients [12,13]. Most recently, a frameshift mutation in the ANP gene was reported in a family of European ancestry [14]. This mutation abolished the stop codon, creating a mutant molecule with 12 extra amino acids at the C-terminus of ANP. The members of this family with the mutant gene developed atrial fibrillation. Some of them also had hypertension that required medical intervention. In an animal model, the mutant ANP was shown to shorten monophasic action potential in cardiomyocytes, which may explain the phenotype of atrial fibrillation in the patients.

In addition to the ANP gene, mutations have also been reported in the ANP receptor gene. For example, an 8-bp deletion was identified in the 5′-flanking region of the ANP receptor gene [15]. This mutation impaired the promoter activity when tested in vitro and was associated with hypertension and cardiac hypertrophy in a group of Japanese patients. These data suggest that genetic mutations affecting the ANP pathway may contribute to hypertension and heart disease in humans.
The cardiac protease corin

In cardiomyocytes, ANP is made as a precursor, pro-ANP. Proteolytic removal of the N-terminal propeptide converts pro-ANP to active ANP. For many years, the enzyme responsible for this activation cleavage remained unidentified. Several years ago, a novel serine protease, corin, was isolated from the human heart [16,17]. Corin is a large protein with 1042 amino acids and heavily glycosylated [17–19]. Topologically, it is a type II transmembrane protease with an N-terminal cytoplasmic tail followed by a transmembrane domain. The rest of the molecule is extracellular, which includes two frizzled domains, eight LDL receptor repeats, one scavenger receptor repeat and a trypsin-like protease domain. Through its transmembrane domain, corin is tethered on the cell surface. This feature distinguishes corin from most of the trypsin-like proteases that are secreted proteins. Corin expression is most abundant in atrial and ventricular cardiomyocytes [17].

Normally, pro-ANP is stored in the dense granules of the myocyte. Pro-ANP activation occurs upon its secretion. In functional studies, corin was shown to cleave pro-ANP at the predicted activation site, converting it to active ANP, as indicated by its activity in stimulating intracellular cGMP production [20–22]. The corin-mediated pro-ANP processing occurred on the cell surface but not inside the cell. Inhibition of corin expression blocked pro-ANP activation in cardiomyocytes [23], indicating that corin is the pro-ANP convertase. This conclusion was supported by studies of corin knockout mice [24]. The mice lacking corin had elevated levels of pro-ANP but not detectable mature ANP in the heart, demonstrating that corin is essential for pro-ANP processing in vivo.

As a newly identified enzyme, corin may have additional substrates that are involved in other biological pathways. For example, corin is expressed in the kidney but its renal function is unclear [17]. In a recent study, corin mRNA and protein were detected in the dermal papilla [25]. Corin knockout mice appeared to have a lighter hair colour than that of wild-type controls [25]. This function of corin in the skin may or may not be mediated by its pro-ANP processing activity, and its biological significance remains to be established.

Corin deficiency and hypertension

The importance of corin in regulating blood pressure has been evaluated. In corin null mice, systolic, diastolic and mean arterial blood pressures were increased compared to that of normal controls [24]. This phenotype is similar to the hypertension observed in ANP null mice [9], consistent with corin being the pro-ANP convertase. When corin null mice were fed a high salt (8%) diet, their blood pressure increased to a higher level than that of controls, suggesting that the ability of these mice to adjust to high salt diets was compromised. Interestingly, when female corin null mice became pregnant, their blood pressure increased dramatically [24]. The mice also had proteinuria at late gestation stages. It appears, therefore, that during pregnancy when blood volume expands, corin becomes critical in preventing high blood pressure under this special circumstance. Further studies will be important to determine if corin deficiency also plays a role in pregnancy-induced hypertension in humans.

In addition to hypertension, corin null mice also had cardiac hypertrophy [24]. This cardiac phenotype was confirmed in a naturally occurring mutant mouse, KitW-sj, in which the corin gene was disrupted by a genetic inversion [26]. It is unclear if this phenotype is secondary to high blood pressure in these mice or due to the loss of an unknown function of corin in modulating cardiomyocyte morphology and structure.

The human corin gene is located on chromosome 4p12-13, which includes 22 exons and spans >200 kb in length [27]. Some of its introns exceed 30 kb. In principle, genetic variations and mutations occur more frequently in large genes. To date, a number of SNPs in the human corin gene have been identified (http://www.hapmap.org). Two non-synonymous SNPs (T555I/Q568P) in a minor corin allele have been found to be more common in African Americans than Caucasians [28]. In epidemiological studies, this minor corin allele was associated with an increased risk for hypertension and an enhanced cardiac hypertrophic response to high blood pressure [28,29]. Patients with this allele had a greater left ventricular mass than that in control patients with wild-type alleles but similar systolic blood pressure. In a most recent study, recombinant corin variant T555I/Q568P was found to have a lower activity in processing natriuretic peptides [30]. The reduction of the activity appeared due to impaired zymogen activation. These data indicate that corin deficiency may contribute to hypertension in humans, especially in African Americans who are known to have a high prevalence of hypertensive disease. It will be interesting to know if these corin variants alter patients’ response to antihypertensive drug treatment.

Conclusion

The natriuretic peptide system is important in controlling blood pressure and salt–water balance. The discovery of corin as the pro-ANP convertase extends our understanding of the ANP pathway. Studies in knockout mice demonstrate that the corin gene is critical for maintaining normal blood pressure. The finding of corin variants in African Americans suggests a potential role of corin in hypertension in humans and encourages more research to identify new corin mutations that may cause disease.

Acknowledgements. The authors wish to thank former and current lab members for their contributions and Dr Martin Schreiber for his support. This work was supported in part by grants from the Ralph Wilson Medical Research Foundation, the Bakken Heart-Brain Institute, the National Institutes of Health (R01 HL089298), and fellowships from Shandong University and Tianjin Medical University in China.

Conflict of interest statement. None declared.
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Received for publication: 1.12.08
Accepted in revised form: 4.12.08