Novel Insights Into the Mechanisms Regulating Pro-Atrial Natriuretic Peptide Cleavage in the Heart and Blood Pressure Regulation

Proprotein Convertase Subtilisin/Kexin 6 Is the Corin Activating Enzyme

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PCSK6-Mediated Corin Activation Is Essential for Normal Blood Pressure
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The biologically active carboxyterminal peptide (αANP), a cardiac hormone that regulates blood pressure through natriuretic, diuretic, and vasorelaxant properties, is released from cleavage of a precursor pro-atrial natriuretic peptide (pro-ANP) form by corin. A recently published study in Nature Medicine identified proprotein convertase subtilisin/kexin 6 (PCSK6), a component of the PCSK protease family, as the natural corin activating enzyme. This key processing step of pro-ANP seems to contribute to blood pressure homeostasis and hence to hypertension development.

αANP, a component of the cardiac natriuretic peptide family, is one biologically active product of a larger prohormone whose cleavage generates the α-C-terminal peptide 1–28 and the N-terminal ending 1–98.1 Several physiological experiments have shown that αANP is a key regulator of systemic blood pressure through its natriuretic, diuretic, and vasorelaxant properties.1 In addition, Nppa gene knock-out leads to salt-sensitive hypertension in mice.2 Lack of type A natriuretic peptide receptor, the cyclic guanosine monophosphate coupled receptor mediating αANP actions, also causes hypertension in mice.3 Consistently, functional variants of human ANP gene have been demonstrated to contribute to high blood pressure development as well as to its common cardiovascular complications.4 The combined pathophysiological and genetic evidence, not commonly shared by other hormones of the cardiovascular system, support the long and extensive search efforts to introduce innovative therapeutic approaches to treat hypertension by raising αANP levels.5

Corin is the known pro-ANP activating enzyme in the heart.5 A proper corin activation is needed to guarantee adequate ANP activity in the body. In turn, corin deficiency seems to be a critical defect that predisposes to hypertension development and heart disease.6 Moreover, corin overexpression is beneficial in experimental heart failure.8

A recent study published in Nature Medicine9 finally reveals that PCSK6, a protease belonging to the PCSK family, is the long searched specific corin activating enzyme and, as such, a critical regulator of the whole cascade leading to pro-ANP processing and to αANP release into the circulation, ultimately controlling water–electrolyte and blood pressure homeostasis.

Preliminary studies demonstrated that, among several protease inhibitors, only the PCSK inhibitors are able to inhibit corin activation. The subsequent identification of the specific corin activating enzyme was achieved through the overexpression of each of the 9 PCSK family members in HEK293 cells expressing human corin. It was observed that only PCSK6 enhanced corin activation. On the other hand, selective PCSK6 gene silencing by small interfering RNAs abolished corin activation cleavage in the same cell line and in HL-1 cells. Furthermore, PCSK6 gene expression was detected in all cell lines expressing corin, including those of the human heart. Both the corin cleavage site (Arg801) and the cellular processing site (cell surface), where corin becomes activated by PCSK6 in the heart, were identified in this investigation. Accordingly, corin variants lacking the cleavage site for PCSK6 were shown to be resistant to PCSK6 activation.

In the same study, the in vitro data were reinforced by ad-hoc in vivo experiments. In particular, lack of PCSK6 in mice led to impaired corin activation, decreased pro-ANP processing, and development of hypertension.9

The specificity of corin for pro-ANP cleavage is an intriguing result of the study.9 In fact, pro-brain natriuretic peptide (BNP) levels were left unaltered by lack of either corin or PCSK6, although previous evidence have shown that corin has pro-BNP processing properties.8 Interestingly, in spite of the PCSK6-corin independent processing of pro-BNP, active BNP was unable to counteract the critical lack of the antihypertensive effect of αANP. Thus, the predominant role of αANP in controlling blood pressure is an important by-product of this investigation and supports previous findings. Also in this experimental setting, high salt dietary feeding exacerbates the hypertensive condition consistent with αANP being a regulator of salt excretion in the kidneys.

Surprisingly, no prohypertrophic effect was detected in the Pcsk6 knock-out mice, and cardiac function was unchanged.

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This evidence appears to be in contrast with the established knowledge that lack of ANP,\(^{1}\) of type A natriuretic peptide receptor,\(^{4}\) as well as of corin\(^7\) leads to left ventricular hypertrophy. In fact, ANP plays significant antihypertrophic effects in the heart through several mechanisms, including regulation of transforming growth factor-\(\beta\) signaling.\(^{11}\) It is likely that some of the factors under PCSK6 control may counteract the pro-hypertrophic effect of \(\alpha\text{-ANP}\) deficiency. As suggested by the authors, a still unexplored interaction of PCSK6 with transforming growth factor-\(\beta\) in the heart may provide a plausible explanation.

The potential contributory role of PCSK6 to the development of human hypertension needs to be characterized. In this regard, the authors provide some indirect evidence by showing that a PCSK6-mediated processing of corin is reduced in the presence of corin variants (T555I and Q568P) previously associated to hypertension and to heart disease in blacks,\(^{12}\) as well as in the presence of corin variants (K317E, S472G, and R539C) previously identified in patients with preeclampsia and hypertension.\(^{9}\) A glimpse into genetics of human hypertension was attempted through the PCSK6 gene sequencing analysis of 100 hypertensive patients, and it suggested that PCSK6 genetic variants that reduce corin activation (such as D282N) may contribute to hypertension development. Of note, this observation is consistent with recent studies performed in Chinese where an increased linkage to blood pressure was attempted through the PCSK6 gene sequencing.\(^{13}\) Of note, this observation is consistent with recent studies performed in Chinese where an increased linkage to blood pressure was attempted through the PCSK6 gene sequencing.\(^{13}\) However, the importance of PCSK6 discovery relies also on the fact that this protease is part of the PCSK family. The latter includes a class of enzymes that belong to the serine endoprotease superfamily, which catalyzes the hydrolytic cleavage of several molecular substrates. Of note, other known substrates of PCSK6 are cytokines of transforming growth factor-\(\beta\) family, the NODAL (nodal growth differentiation factor) proprotein, and aggrecanases that lead to aggrecan breakdown, thus implying a role in the central nervous system patterning and left–right axis formation, as well as in osteoarthritis.\(^{13}\) Interestingly, PCSK9, another component of the PCSK family, is a ligand of low-density lipoprotein cholesterol receptor and a mediator of its degradation, and it has recently been identified as the target of an innovative therapeutic approach to reduce hypercholesterolemia and cardiovascular risk.\(^{14}\)

A Step Forward for ANP-Based Therapy in Hypertension?

An increasing number of consistent findings, reinforced by the current novel evidence,\(^9\) suggest that ANP-based therapies would greatly contribute to improve treatment of human hypertension. However, no ANP-based treatment has yet become available to the medical community mainly due to either peptide instability or to the undesired side effects of neutral endopeptidase blockade. The upcoming pharmacological approach that uses ANP degrading enzyme, neprilysin, as a rational way to raise ANP levels seems to be promising.\(^{15}\) With this approach, the parallel activation of the angiotensin II requires to be counteracted by concomitant blockade.

The current discovery of the corin activating enzyme, although improving our understanding of ANP regulatory mechanisms and of its functions, may offer the opportunity of novel therapeutic approaches. Once the role of PCSK6 will be better dissected out in human hypertension, PCSK6 may become itself a reasonable target for the development of drugs able to control high blood pressure by directly modulating pro-ANP cleavage and, therefore, increasing endogenous circulating \(\alpha\text{-ANP}\) levels. Such a therapeutic approach may reveal beneficial also in the treatment of heart failure.

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