Department of Medicine, Solna

Relevance of the salt-inducible kinase network
for the development of high blood pressure and cardiac hypertrophy

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av

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Hypertension (high blood pressure) is a multifactorial condition that remains a big worldwide problem. 95% of all hypertensive people suffer from essential hypertension with unknown causes. This can cause different heart diseases such as cardiac hypertrophy (CH), a condition which can ultimately lead to heart failure. Salt intake has been suggested to be one of the factors promoting hypertension. The aims of this thesis were to elucidate the importance of salt-inducible kinase 1 (SIK1) in the development of high blood pressure (BP) and to identify salt-activated molecular pathways that could activate transcription factors and genes coupled with development of CH independently of high BP.

SIK1 has been implicated in intracellular pathways that control cell sodium homeostasis and is also important for myocyte development. To investigate whether SIK1 is a potential regulator of BP, genotype-phenotype association studies between a genetic variation within SIK1 coding region (rs3746951) and BP in four population-based cohorts were performed. After performing a meta-analysis of the four studies the results revealed an association between the rs3746951 and lower systolic- and diastolic blood pressures. Rs3746951 was also associated with lower left ventricular mass. In studies performed in cultured vascular smooth muscle cells it was shown that rs3746951 was associated with higher SIK1 and Na+/K+-ATPase activity. These results suggest that SIK1 affects BP.

To explore the involvement of SIK1 in the development of CH, studies were performed in a mouse cardiac atrium cell line (HL-1). The overall results revealed that SIK1 mediated the effect of salt on transcription factors MEF2 and NFAT and on the genes associated with CH: Mhc Bnp and Ska. Studies performed on samples from human biopsies confirmed the association between SIK1 and hypertrophic genes. These results suggest that salt intake could trigger events that lead to increased expression levels of genes associated with CH, independently of increases in BP and that SIK1 is a mediator of this process.

Since SIK1 can affect the transcription of genes that are associated with CH, the involvement of a hypertensive form of α-adducin and SIK isoforms in this process was examined. mRNA levels for SIK2, α-adducin, and several markers of CH were correlated in tissue biopsies obtained from human hearts. Evidence that SIK2 is critical for the development of CH in response to chronic high-salt diet was also obtained in mice with ablation of the Sik2 gene. Increases in heart size upon high salt diet, occurred only in Sik2+/+ but not in Sik2−/− mice. The presence of a hypertensive variant of α-adducin in Milan rats (before they become hypertensive) was associated with elevated transcription factors and genes associated with CH. Thus, we concluded that CH, triggered by salt intake or the presence of a genetic variant of α-adducin, requires SIK2 and is independent of elevated BP.

Taken together, this thesis describes how the SIK network could affect BP regulation and independently of BP mediate the effect of salt on the development of CH.