Involvement of salt-inducible kinase (SIK) family enzymes in diabetes and hypertension

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Summary

The cloning of salt-inducible kinase-1 (SIK1) that was specifically expressed in the adrenal glands of high-salt diet-fed rats led to subsequent clonings of adipose-specific SIK2 and rather ubiquitous SIK3. The three enzymes constitute a novel serine/threonine kinase subfamily, a member of AMP-activated protein kinase family. Physiological roles of SIK1 and SIK2 have been investigated. The SIK1 transcript was expressed very early in the ACTH-stimulated Y1 cells, even before the expression of transcripts for CYP11A and StAR protein. Forced expression of SIK1 inhibited the ACTH-dependent expression of CYP11A- and StAR protein-genes. Cotransfection assays employing CRE-reporter gene showed that SIK1 could repress the PKA-dependent activation of CRE by acting on the CREB's bZIP domain, though the target site of SIK1-mediated phosphorylation has yet to be determined. The ACTH/PKA-dependent nucleocytoplasmic shuttling of SIK1 took place in Y1 cells, implicating that the intracellular movement of SIK1 might be a physiologically important determining factor for regulation of steroidogenic gene expression in the early phase of ACTH-stimulation. The SIK2 gene was expressed in 3T3-L1 cells at a very early stage of adipogenesis. SIK2 could phosphorylate Ser-794 of human Insulin-Receptor-Substrate-1 *in vitro* as well as *in vivo*. Besides, the SIK2 activity in *db/db* mice adipose tissues was significantly higher than that in wild-type adipose. These results strongly suggest that SIK2 may play important role(s) in modulating the insulin-signaling cascade of adipocytes, and thus, may be involved in the development of insulin resistance. Taken together, these results suggest that the SIK isoforms regulate hormonal signal transductions in adrenal as well as in fat tissues.