Regulation of epithelial sodium channel by Akt and Sgk

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Activity of the epithelial sodium channels (ENaC) in the kidney plays an important role in sodium/fluid homeostasis and the maintainance of blood pressure. Sodium transport *via* ENaC is upregulated by the hormones aldosterone and insulin. It has been suggested that aldosterone may act on ENaC *via* the serum and glucocorticoid-dependent protein kinase, Sgk. In this study, we investigate the role of Sgk and the closely related protein kinase, Akt, in regulating ENaC activity in Fisher Rat Thyroid (FRT) cells. We found that expression of either Sgk or Akt significantly increased sodium current in FRT cells transfected with ENaC whereas expression of either dominant negative constructs or small interfering RNA (siRNA) directed against Sgk or Akt significantly decreased ENaC activity. In addition, siRNA against Akt and Sgk abolished the stimulatory effects on ENaC activity of insulin and of over-expression of the enzymes PI3K or PDK. Interestingly, co-transfection of siRNA against Akt and siRNA against Sgk had an additive inhibitory effect on ENaC activity. Our data further suggest that the actions of Akt and Sgk actions on ENaC activity were dependent on the ubiquitin protein ligase Nedd4-2. Expression of either Akt or Sgk partially overcame the inhibitory effect of Nedd4-2 on ENaC activity. In addition, mutation in Nedd4-2 of S342A and S428A, which are consensus phosphorylation sites for Akt and Sgk, abolished the stimulatory effect of Akt and Sgk expression on ENaC. Taken together, our findings suggest that insulin upregulates ENaC activity *via* a pathway that involves PI3K and PDK and that Sgk and Akt are downstream effectors of this regulatory pathway. When activated, Akt and Sgk phosphorylate Nedd4-2 and render it unable to interact with and downregulate ENaC activity.