Regulation of the epithelial sodium channels

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The epithelial Na^+ channel (ENaC) plays an important role in the regulation of extracellular fluid volume and blood pressure and in the regulation of the volume of the fluid bathing the apical surfaces of epithelia such as the respiratory and reproductive epithelia (Voilley *et al.*, 2002). Given that ENaC represents a passive pathway for Na^+ to diffuse from the external environment into the cells, it also represents a significant mechanism by which changes in the sodium composition of the external environment, such as in the lumen of the kidney distal collecting tubule or in the lumen of salivary ducts, influences the cytosolic composition and volume of epithelial cells.

ENaC is subject to a wide range of regulatory mechanisms. These regulatory systems include the mineralocorticoid hormone aldosterone, growth factors such as insulin and IGF-I and cytokines such as TNF-α as well as the feedback mechanisms that regulate the activity of the channels in response to changes in intracellular Na^+ and intracellular Cl^- (Dinudom *et al.*, 2002). In addition to these systems, the activity of ENaC is also known to be modulated by the Cl^- channel, cystic fibrosis transmembrane conductance regulator (Stutts *et al.*, 2002). Some of the systems that modulate the activity of ENaC have intracellular pathways in common. A good example of this is the relationship between aldosterone regulation and the feedback regulation of ENaC. It has been suggested that the early effects of aldosterone, on the activity of ENaC are mediated by suppression of the Na^+ feedback regulatory system. This is proposed to operate by aldosterone increasing the expression of the serum and glucocorticoid-dependent protein kinase, Sgk, which phosphorylates the ubiquitin protein-ligase Nedd4-2, a principal mediator of the Na^+ feedback system, so as to render it unable to interact with ENaC (Snyder *et al.*, 2002). Although the effect of Sgk on ENaC activity has been demonstrated for ENaC expressed in *Xenopus* oocytes, this phenomenon has not been observed in either isolated mouse mandibular duct cells or M1 mouse collecting duct epithelia. Interestingly, we have found that the activity of cytosolic kinases other than Sgk is essential for the maintenance of the basal activity of ENaC and that when activated, these kinases inhibit the Na^+ feedback regulatory system. It is conceivable that these protein kinases may also be involved in the mechanism by which aldosterone upregulates ENaC activity.

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