EXPANDED ABSTRACT

Proteolytic activation of the epithelial sodium channel (ENaC) in health and disease

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The epithelial sodium channel (ENaC) is a member of the ENaC/degenerin family of non-voltage gated ion channels. ENaC is localized in the apical membrane of epithelial cells, and is the rate limiting step for sodium absorption in a number of epithelial tissues like the aldosterone-sensitive distal nephron (ASDN), respiratory epithelia, distal colon, sweat and salivary ducts. ENaC is probably a heterotrimer with three well characterized subunits ($\alpha\beta\gamma$). In humans an additional δ-subunit (δ-hENaC) exists but little is known about its function.

The regulation of ENaC is highly complex (1) and proteolytic processing of ENaC is thought to contribute to its activation under physiological and pathophysiological conditions (2-4). Proteases contribute to ENaC regulation by cleaving specific sites in the extracellular loops of the α- and γ-subunits but not the β-subunit. The channel is thought to be in its mature and active form in its cleaved state, but there is evidence for the presence of both cleaved and non-cleaved channels in the plasma membrane. Cleavage may activate the channel by changing its conformation probably by releasing inhibitory peptides from the extracellular loops of α- and γ-ENaC.

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Airway-specific over-expression of the β-subunit of ENaC has recently been shown to cause airway surface liquid depletion and cystic fibrosis (CF) like lung disease (5). In the kidney ENaC is critically important for the maintenance of body sodium balance (1). This is evidenced by gain of function mutations of ENaC which cause a severe form of arterial hypertension known as Liddle's syndrome. Loss-of-function mutations of ENaC cause pseudohypoaldosteronism type I (PHA1), a disease characterized by renal salt wasting. Patients with PHA1 may also suffer from respiratory symptoms similar to those of patients with atypical CF. In PHA1 a reduction of ENaC-mediated Na^+ absorption in respiratory epithelia is thought to favor fluid secretion in the respiratory tract (6).

These examples illustrate the importance of ENaC function and the need for an appropriate regulation of ENaC activity in a tissue specific manner. Most of our knowledge about ENaC activation by extracellular proteases stems from studies in model system like *Xenopus laevis* oocytes (7) and cultured cells. Recently, functional evidence is emerging that ENaC activation by extracellular proteases can occur in native tissue (8). Inappropriate ENaC activation by endogenous proteases may be involved in sodium retention in nephrotic syndrome (9) and may aggravate symptoms of cystic fibrosis during acute respiratory infections associated with the generation of local proteases. Moreover, ENaC may be a modifier gene in patients with cystic fibrosis. Indeed, ENaC polymorphisms with a gain-of-function and a loss-of-function effect have been identified

in patients with atypical CF (10). At present it is unclear why some loss-of-function mutations of ENaC mainly manifest as a renal salt wasting syndrome (PHA1) while others cause CF-like pulmonary symptoms without overt renal disease. Organ specific differences in ENaC processing and activation and differences in the genetic background may be responsible for the development of different disease phenotypes.

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