Role of proteases in the activation of epithelial Na^+ channels

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Epithelial sodium channels (ENaCs) are expressed at the apical plasma membrane of high resistance Na^+ transporting epithelia. These channels have key roles in the regulation of extracellular fluid volume, blood pressure, and airway surface liquid volume. ENaCs are composed of three homologous subunits, termed α, β, and γ. These subunits share a common structure with two membrane-spanning domains separated by a large ectodomain, and cytosolic amino and carboxyl termini. Maturation of ENaC subunits involves furin-dependant proteolytic cleavage of the extracellular loops at specific sites within the α and γ subunits. ENaC subunit proteolysis activates channels by dramatically increasing open probability. The α subunit is cleaved twice by furin, releasing an inhibitory peptide. Channels that are not cleaved by proteases have a low open probability due to inhibition by external Na^+. Both cleaved and non-cleaved channels are expressed at the plasma membrane, suggesting that a population of channels that escapes processing by furin may be cleaved and activated by proteases within the apical membrane or within luminal fluids. It is likely that a variety of proteases, in addition to furin, have an important role in the proteolytic processing and activation of ENaCs.