

Role of proteases in the activation of epithelial Na⁺ channels

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(Introduced by David Cook)

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.