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The epithelial Na^+ channel ENaC – a crucial protein in many diseases

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Epithelial Na^+ channels (ENaC) are located in the luminal membrane of salt absorbing epithelia in kidney, airways, colon and glandular excretory ducts. ENaC has been identified as the crucial protein with a central role in several diseases. In distal lung epithelia, ENaC controls fluid absorption at the air–liquid interface, thereby determining the rate of mucociliary clearance. Increased Na^+ absorption due to gain of function mutations of ENaC may lead to hypertension and decreased mucociliary transport as in cystic fibrosis. Cystic fibrosis is characterized by a loss of cAMP-activated cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- conductance and enhanced Na^+ absorption in airways and colon. Abnormally low ENaC activity causes severe renal salt-loss syndromes and hypotension, high altitude pulmonary oedema in adults and a respiratory distress syndrome in newborns. Recently ENaC was found to be the target for acute infections by respiratory viruses, which may contribute to enhanced secretion and the wet lung phenotype in influenza virus infections. ENaC activity, which is primarily regulated by Nedd4-2-dependent ubiquitination, involving phosphorylation by the serum glucocorticoid kinase, is also controlled by CFTR and other Cl^- channels. Inhibition of ENaC during activation of CFTR has been demonstrated in numerous tissues and is probably mediated by an increase in the intracellular Cl^- concentration. ENaC is also inhibited by activation of purinergic receptors, as demonstrated in airways and renal cells. The inhibitory effect is independent of intracellular Ca^{2+} or Ca^{2+}-dependent protein kinase C (PKC). However, it requires the function of phospholipase C and involves Cl^- transport over the luminal membrane. Since ENaC activity depends on the interaction with phosphatidylinositols such as PIP_2, ATP or UTP inhibit ENaC most probably by hydrolysis of PIP_2. Both CFTR and purinergic inhibition of Na^+ absorption are Cl^- dependent and we may therefore hypothesize a Cl^--sensitive site in one or several subunits of the epithelial Na^+ channel.