Regulation of the epithelial Na^+ channel (ENaC) by kinases

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Activity of the amiloride-sensitive epithelial Na^+ channel (ENaC) in the distal nephron and respiratory tract has a profound impact on Na^+ homeostasis, the regulation of blood pressure and respiratory surface fluid volume. Dysfunction of ENaC is a feature of human diseases such as Liddle's syndrome, pseudohypoaldosteronism type 1 and cystic fibrosis. The activity of ENaC is tightly controlled by an array of physiological factors that exert their effect on transcription, trafficking and gating of the channel *via* multiple cellular signalling pathways. In the past decade, protein kinases that are involved in these signalling pathways have been identified and their therapeutic potential for treating diseases with ENaC dysfunction has been explored. MAP kinase signalling is known to be involved in the cellular signalling pathway by which growth factors downregulate expression and activity of ENaC. Recent studies from our laboratory suggest that EGF employs the canonical MAPK signalling pathway, Ras/Raf/MEK/ERK, to inhibit activity of ENaC. We found that H-Ras, but not K-Ras, is the small GTPase that mediates this effect of EGF on ENaC and that H-Ras inhibits activity of ENaC without altering the number of channels in the cell membrane. PDGF signalling regulates ENaC, on the other hand, by a mechanism that ERK1/2-dependent but does not involve H-Ras. This signalling pathway is mediated *via* c-Src, which increases ERK1/2-dependent inhibition of the channel. During oxidative stress, reactive oxygen species inhibit activity of ENaC by a p38 MAP kinase-dependent mechanism. Unlike ERK1/2, the p38 signalling inhibits proteolytic activation and expression of ENaC subunits. These findings suggest the importance of multiple MAP kinase signaling mechanisms in the regulation of transepithelial Na^+ absorption *via* ENaC.