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Title: Mechanism of epithelial Na^+ channel (ENaC) inhibition by hypoxia in alveolar epithelial cells

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Body: Introduction: Transepithelial sodium transport via alveolar epithelial Na^+ channels (ENaC) and Na,K-ATPase constitutes the driving force for removal of alveolar oedema fluid. However, alveolar hypoxia associated with pulmonary edema may impair ENaC activity in alveolar epithelial cells (AEC). Methods: We studied the mechanism of hypoxia-induced decrease in ENaC activity and alveolar Na^+ absorption in vitro in rat AEC and in vivo in β-Liddle mouse strain harbouring a mutation within the β-ENaC gene abolishing the interaction between ENaC and the ubiquitin protein-ligase Nedd4-2 that targets the channel for endocytosis and degradation in the proteasome. Results: In vitro, acute exposure of AEC to hypoxia (0.5% O2 for 1-6h) rapidly decreased transepithelial Na^+ transport as assessed by equivalent short-circuit current Ieq and the amiloride-sensitive component of Na^+ current across the apical membrane, reflecting ENaC activity. Hypoxia reduced the expression of α-, β- and γ-ENaC proteins in the plasma membrane, with no change in intracellular expression. Hypoxia-induced inhibition of amiloride-sensitive Ieq was rapidly reversed by the β2-agonist terbutaline, and was fully prevented by preincubation with proteasome inhibitors. In vivo, hypoxic exposure (8% O2 for 24h) reduced amiloride-sensitive alveolar fluid clearance by 69% in wild-type mice without changing the expression level of ENaC proteins in the distal lung, but had no significant effect in homozygous mutated Liddle mice. Conclusion: These data strongly suggest that decreased cell surface expression of ENaC subunits under hypoxic condition is related to Nedd4-2-mediated endocytosis of ENaC and subsequent degradation in the proteasome.