

Abstract

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Influenza virus M2 protein inhibits epithelial sodium channels by increasing reactive oxygen species.

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BACKGROUND: The mechanisms by which replicating influenza viruses decrease the expression and function of amiloride-sensitive epithelial sodium channels (ENaCs) have not been elucidated.

OBJECTIVE AND METHODS: We show that expression of M2, a transmembrane influenza protein, decreases ENaC membrane levels and amiloride-sensitive currents in both *Xenopus* oocytes, injected with human alpha-, beta-, and gamma-ENaCs, and human airway cells (H441 and A549), which express native ENaCs.

RESULTS: Deletion of a 10-aa region within the M2 C terminus prevented 70% of this effect. The M2 ENaC down-regulation occurred at normal pH and was prevented by MG-132, a proteasome and lysosome inhibitor. M2 had no effect on Liddle ENaCs, which have decreased affinity for Nedd4-2. H441 and A549 cells transfected with M2 showed higher levels of reactive oxygen species, as shown by the activation of redox-sensitive dyes. Pretreatment with glutathione ester, which increases intracellular reduced thiol concentrations, or protein kinase C (PKC) inhibitors prevented the deleterious effects of M2 on ENaCs.

CONCLUSIONS: The data suggest that M2 protein increases steady-state concentrations of reactive oxygen intermediates that simulate PKC and decrease ENaCs by enhancing endocytosis and its subsequent destruction by the proteasome. These novel findings suggest a mechanism for the influenza-induced rhinorrhea and life-threatening alveolar edema in humans.

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