J Physiol 591.15 (2013) pp 3675–3676

The Journal of Physiology

PERSPECTIVES

Being positive: revisiting the elevated sodium permeability hypothesis in cystic fibrosis

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Cystic fibrosis (CF) is a devastating lung disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) anion channel. Reduced CFTR channel activity leads to defective salt and water secretion by the submucosal glands that empty into the airways and changes in the composition and depth of the thin fluid layer covering the airway surface (airway surface liquid, or ASL). These alterations in the ASL compromise mucociliary clearance and increase susceptibility to bacterial infections in the airways.

For over 25 years it has been argued that CFTR dysfunction also leads to an increase in the apical sodium permeabilities of epithelial cells on the airway surface (Boucher *et al*. 1988). An increase in sodium permeability would be expected to enhance salt and water reabsorption across airway surface epithelia and contribute to reductions in ASL volume and mucociliary clearance. How CFTR dysfunction might lead to enhanced apical sodium permeability is unknown but conceivably involves a secondary effect on the activities or numbers of epithelial sodium channels (ENaCs) in the apical membranes of these cells. If true, the sodium permeability hypothesis implicates ENaC regulation as a potential drug target for treating CF lung disease.

The proposal that apical sodium permeability is elevated in CF airway epithelia is based largely on the finding that amiloride, a fairly specific ENaC inhibitor, has substantially greater effects on the electrical properties of CF *versus* normal airway epithelia, in particular on the transepithelial voltage measured under open-circuit conditions and on transepithelial short-circuit currents measured under voltage clamp conditions (e.g. Boucher *et al*. 1988). These greater effects of amiloride are consistently observed across laboratories for both freshly excised and cultured CF airway epithelia. But do they reflect actual increases in the apical sodium permeabilities of CF airway epithelial cells? Two arguments, one theoretical and the other experimental, have been offered to counter the elevated sodium permeability hypothesis. The theoretical argument derives from an equivalent electrical circuit analysis which predicts that a reduced apical chloride permeability (e.g. due to a loss of CFTR function) will by itself enhance the effects of amiloride on the electrical properties of an epithelium without an increase in sodium permeability (Horisberger, 2003). This secondary effect on the amiloride response is due to electrical coupling between the fluxes of sodium and chloride across the apical membrane with changes in chloride permeability affecting the electrochemical driving force for sodium flux (and vice versa). The experimental argument against the sodium permeability hypothesis is supported by detailed studies of cultured and excised airway epithelia obtained from CFTR knockout pigs. Transepithelial sodium fluxes across these tissues are not increased in CF pigs, which like CF patients exhibit defective bacterial clearance from the lung (Chen *et al*. 2010). Subsequent studies of epithelial cells cultured from the large airways of CF patients also failed to show increases in transepithelial sodium fluxes or of apical sodium permeability (Itani *et al*. 2011). These findings call into question the importance of elevated sodium reabsorption at least in the models and tissues that were examined.

In this issue of *The Journal of Physiology* O'Donoghue *et al*. (2013) revisit the sodium permeability hypothesis by performing detailed mathematical simulations of the transport properties of normal and CF nasal epithelia. The authors chose primary cultures of human nasal epithelia for their modelling because of the extensive amount of transport data available in the literature and because the transepithelial voltage across the nasal epithelium (nasal potential difference or nasal PD) and its response to amiloride are abnormal in CF patients. Indeed, the nasal PD assay is a benchmark for assessing disease severity and the efficacy of candidate CF drugs. Their simulation results show convincingly that the apical sodium permeabilities of CF nasal epithelia must be increased given the transport parameters that are in the literature. The authors' findings also confirm that the electrical responses to amiloride are determined in part by the magnitude of the apical chloride permeability, as predicted by the equivalent electrical circuit analysis noted above. But this effect is not sufficient to account for the much larger effects of amiloride on the transport properties of CF nasal epithelia. Only a higher apical sodium permeability can explain the greater amiloride responses of CF nasal epithelia.

How do we reconcile the interesting simulation results of O'Donoghue *et al.* with the lack of experimental evidence for sodium hyperabsorption in the studies noted above? It seems clear that the simulations were performed rigorously. Multiple simulations were performed over a range of transport parameter values with particular attention paid to potential sources of error and to the sensitivity of model outputs to variations in these parameter values. Even if the published transport parameters that were used as input data are only approximately correct, the errors in these data are unlikely to be sufficient to invalidate the authors' conclusion of a higher apical sodium permeability in CF nasal epithelia. The experimental studies cited above were performed in different species (pig) and/or using different tissues (human large airways). Perhaps an elevation in apical sodium permeability is specific to the nasal epithelia of human CF patients. Whatever the reasons for this disparity, the modelling results of O'Donoghue *et al*. (2013) breathe new life into the sodium permeability hypothesis in CF. How mutations in an anion channel (CFTR) could lead to secondary increases in ENaC function in certain tissues continues to be an open but fascinating question.

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DOI: 10.1113/jphysiol.2013.260406

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Competing interests

None.

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