Advances in Pharmacological Treatment of Cystic Fibrosis

av

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Abstract


Cystic fibrosis (CF) is an inborn, hereditary disease, due to mutations in the gene for a cAMP-activated chloride (Cl⁻) channel, the cystic fibrosis transmembrane conductance regulator (CFTR). As a result of impaired ion and water transport, the airway mucus is abnormally viscous, which leads to bacterial colonization. Recurrent infections and inflammation result in obstructive pulmonary disease. Similar changes in the pancreas lead to pancreatic insufficiency.

Several compounds have been tested to improve transepithelial ion transport in CF patients, either via activation of the mutant CFTR, or via stimulation of alternative chloride channels. The main purpose of this thesis was to find substances that might correct the defective ion transport in epithelial cells in CF and could be useful for the pharmacological treatment of CF patients.

Long-term treatment with the macrolide antibiotic azithromycin (AZM) improved clinical parameters and lung function in CF patients and increased Cl⁻ transport in CF bronchial epithelial cells (CFBE) (Paper I); although mRNA expression of the CFTR gene remained unchanged.

In contrast, pre-exposure to the mucolytic antioxidant N-acetylcysteine (NAC) increased CFTR protein expression and was associated with increased Cl⁻ efflux from CFBE cells (Paper II). Clinical trials of this substance might be warranted.

Duramycin has been the subject of clinical trials that finished in June 2009. Up till now, no results from this study are available. The effect of this substance on Cl⁻ efflux from three CF and three non-CF cell lines (Paper III) was disappointing. An effect was found only in CFBE cells, the effect was minimal, occurred in a narrow concentration range, and was not associated with an increase in the intracellular calcium concentration \([Ca^{2+}]\).

The fact that NO-donors stimulated Cl⁻ efflux from CFBE cells (but did not change \([Ca^{2+}]\)) after several hours of preincubation suggests that these substances may be a potentially interesting group of compounds for the treatment of CF (Paper IV). A model for the effect of NO-donors on Cl⁻ efflux is presented.

Keywords: Cystic fibrosis, CFTR, chloride transport, N-acetylcysteine, NO-donors, duramycin, intracellular calcium, azithromycin.

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