Abstract

Stimulation of human bronchial epithelial cells by GnRH : effect on CFTR-mediated ion transport

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes a cAMP-stimulated chloride channel. CFTR is primarily located at the apical surface of epithelial cells, where its activity is regulated by some protein-protein interactions. As part of new CFTR's partners research, we previously showed that annexin A5 (AnxA5) binds directly to both normal and F508del-CFTR. Moreover, under and overexpression strategies led us to establish a functionnal link between these two proteins. In fact, CFTR-dependent ion secretions are correlated to the intracellular level of AnxA5. Otherwise, in transfected epithelial cells, AnxA5 overexpression increases CFTR's level in plasma membranes and raises CFTR-mediated currents in F508del-CFTR expressing cells.

In the light of these findings, AnxA5 appears as a potential target in order to correct some defects caused by the F508del mutation. A therapeutic approach would be to find some compounds capable of increasing AnxA5 expression in F508del-CFTR expressing epithelial cells. Reviewing the literature, our choice fell on GnRH (gonadotropin-releasing hormone), a commonly used molecule for diverse clinical applications for 25 years. So, the effects of GnRH on the modulation of AnxA5 expression and on CFTR-dependent ion transport were assessed in our different cellular models.

Beside the GnRH receptor expression, we show that AnxA5 expression is augmented in all cell lines after one hour incubation with the hormone (1 nM). Moreover, compared to untreated cells, a significant iodide efflux peak is measured in GnRH pretreated cells, which is correlated with an increased cell surface expression of CFTR. It is of interest to note that these observations have been made in CF and non-CF cells.

In our models and according to our stimulation conditions, GnRH treatment enhances AnxA5 intracellular expression and leads to a rise of CFTR-dependent ion secretions. Nevertheless, given the multitude of activated signaling pathways and regulated genes in response to GnRH binding to its receptor, the positive impact on CFTR activity is probably not solely explained by the effect on AnxA5 expression.

Keywords : CFTR, F508del mutation, ion transport, AnxA5, GnRH, GnRH receptor