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CFTR IS NEGATIVELY REGULATED BY GLUCOCORTICOIDS IN ALVEOLAR EPITHELIAL CELLS

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Background and aims: Cystic Fibrosis (CF) is a severe disease based on mutations in the CF transmembrane conductance regulator (CFTR). The hallmark ion transport defects in CF are a diminished Cl^--secretion and Na^+-hyperabsorption. Glucocorticoids are known to increase the function of epithelial sodium channels (ENaC), but little information exists about the impact on CFTR. However, serum and glucocorticoid-dependent kinase 1 (SGK1) supposedly also increases the CFTR-current. Therefore, we sought to analyze the influence of dexamethasone (D) on CFTR.

Methods: Alveolar epithelial cells from rat fetuses were studied using qPCR and Ussing-Chamber-measurements to determine the mRNA-expression and transport activity (I_{SC} $\mu A/cm^2$; Mean±SEM).

Results: SGK1 mRNA-expression was increased by 250% through D (100nM, 24h) and an exposure for 72h resulted in a fivefold increase of mRNA-expression. The D-concentrations of 300nM and 1µM elevated SGK1-expression by tenfold and fifteenfold, respectively. However, the mRNA-expression of CFTR showed a dramatic reduction by 80% through D-treatment for 24h (100nM). An increase of D did not further reduce the CFTR mRNA-expression. The electrophysiological activity of the CFTR-channel showed a diminished current by D (24h) accordingly (I_{forsk} from 2.3±0.12 to 0.97±0.03 and I_{glyb} from 0.47±0.02 to 0.25±0.01). A prolonged exposure of D for 48h and 72h even further decreased the CFTR-current (I_{forsk} to 0,25±0.03 and 0.24±0.03 and I_{glyb} to 0.12±0.02 and 0.09±0.01).

Conclusions: Even though SGK1-expression is increased the results show how strongly glucocorticoid treatment opposes CFTR-expression and activity. Further analysis will investigate the pathways leading to this reduction focussing on SGK1-inhibition and knockdown of the glucocorticoid-stimulated ENaC.