Hyperglycaemia in cystic fibrosis adversely affects BK channel function critical for mucus clearance

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ABSTRACT Large-conductance, Ca2+-activated, voltage-dependent K+ (BK) channel function is critical for adequate airway hydration and mucociliary function. In airway epithelia, BK function is regulated by its γ-subunit, leucine-rich repeat-containing protein 26 (LRRC26). Since patients with cystic fibrosis (CF)-related diabetes mellitus (CFRD) have worse lung function outcomes, this study determined the effects of hyperglycaemia on BK function in CF bronchial epithelial (CFBE) cells in vitro and evaluated the correlation between glycaemic excursions and mRNA expression of LRRC26 in the upper airways of CF and CFRD patients.

CFBE cells were redifferentiated at the air–liquid interface (ALI) in media containing either 5.5 mM or 12.5 mM glucose. BK activity was measured in an Ussing chamber. Airway surface liquid (ASL) volume was estimated by meniscus scanning and inflammatory marker expression was measured by quantitative real-time PCR and enzyme-linked immunosorbent assay (ELISA). CF patients were assessed by 7 days of continuous glucose monitoring (CGM). LRRC26 mRNA expression was measured by quantitative real-time PCR from nasal cells obtained at the end of glucose monitoring.

BK currents were significantly decreased in CFBE cells cultured under high glucose. These cells revealed significantly lower ASL volumes and increased inflammation, including the receptor for advanced glycation endproducts (RAGE), compared to cells cultured in normal glucose. In vivo, nasal cell expression of LRRC26 mRNA was inversely correlated with hyperglycaemic excursions, consistent with the in vitro results.

Our findings demonstrate that hyperglycaemia induces inflammation and impairs BK channel function in CFBE cells in vitro. These data suggest that declining lung function in CFRD patients may be related to BK channel dysfunction.