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Title: Cigarette smoke induces systemic defects in cystic fibrosis transmembrane conductance regulator (CFTR) ion transport

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Body: Cigarette smoke decreases the function of airway epithelial CFTR and is associated with chronic bronchitis, delayed mucociliary transport, and airways obstruction, pathology similar to CF. CS is also associated with CF-related systemic disorders like diabetes mellitus, pancreatitis, and male infertility and suggesting a potential pathogenic role for CFTR defects. Here, we characterized the systemic CFTR dysfunction caused by cigarette smoke in vivo and in vitro. METHODS: Demographics, spirometry, exercise tolerance, symptom questionnaires, CFTR genetics and sweat chloride analysis were obtained. CFTR activity was measured in human bronchial epithelial cells (HBE) and murine tissues in modified Ussing chambers. Serum acrolein levels were estimated with mass spectroscopy. RESULTS: Healthy smokers (31mEq), COPD smokers (30 mEq) and COPD former smokers (24 mEq) had elevated sweat chloride levels compared to normal controls (14 mEq). These results reflect compromised CFTR activity in a non-pulmonary organ. CFTR activity was decreased in HBE cells exposed to plasma from smokers by 68%, suggesting a circulating factor could confer CFTR dysfunction. Cigarette smoke exposed mice had decreased CFTR activity by NPD (28.9% of controls), tracheal Isc (53%) and intestinal Isc (84.3% and 45%, after 5 and 17 weeks, respectively). Acrolein, a reactive component of CS, was higher by 35% in smokers. In HBEs and mice, acrolein reduced CFTR function, probably of channel opening (Po) and N-acetyl cysteine attenuated these effects. CONCLUSIONS: Cigarette smoke causes a systemic CFTR dysfunction and provides potential explanation for the incidence of CFTR-associated disorders in smokers.