CP009

Topical metformin inhibits chloride secretion but not sodium absorption across human nasal epithelium

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Background: In cystic fibrosis (CF), mutations of the cystic fibrosis transmembrane regulator (CFTR) lead to reduced chloride secretion and increased sodium absorption across airway epithelium. Depletion of airway surface liquid (ASL) volume reduces mucociliary clearance, causing recurrent infection. Reversal of these transport abnormalities is a treatment target in CF.

The metabolic sensor AMP-activated kinase (AMPK) inhibits sodium transport through epithelial sodium channels (ENaC) and chloride transport through CFTR (Myerburg et al, Am J Respir Cell Mol Biol. 2010;42:676-84). AMPK is activated by metformin, a drug commonly used in type II diabetes mellitus to lower blood glucose.

Aims: To determine effects of the AMPK-activating drug metformin on sodium absorption and chloride secretion across human nasal epithelium, using nasal potential difference as an in vivo measure of transepithelial ion transport.

Methods: Participants were healthy volunteers. Exclusion criteria included: nasal disease, cystic fibrosis, diabetes mellitus and pregnancy. The study was approved by the National Research Ethics Committee and all participants gave written, informed consent. Nasal PD was measured between nasal and subcutaneous electrodes after 5 minutes nasal perfusion with: Ringer’s (baseline); Ringer’s amiloride (10^{-4}M) (sodium absorption); Cl^{-} free Ringer’s amiloride (10^{-4}M); Cl^{-} free Ringer’s amiloride (10^{-6}M) isoprenaline (2.5x10^{-5}M) (chloride secretion). In two randomised cross-over studies sodium and chloride secretion were assessed a) in the presence or absence (control) of 10^{-1}M metformin (n=8) and b) in the presence of 10^{-1}, 10^{-3} or 10^{-6}M metformin (n=6). Repeat PD measurements were made at least 48 hours apart.

Results: a) The nasal epithelium was depolarised from baseline by: Metformin 10^{-1}M, 34% (12-57) (median (interquartile range); Ringer’s, -1% (-11-19) (p=0.263). Amiloride-sensitive PD as percent of baseline was: control, 65% (60-92); metformin 10^{-1}M, 54% (16-71), p=0.208. Chloride secretion was: control, 23.8mV (15.6-38.4); metformin 10^{-1}M, 7.8mV (-0.6-11) (p=0.012).

b) Metformin depolarised the nasal epithelium from baseline by: 10^{-1}M, 13% (-6-30); 10^{-3}M, -2% (-11-13); 10^{-5}M, -8% (13-43). Amiloride-sensitive PD as percent of baseline was: 10^{-1}M, 53% (35-84); 10^{-3}M, 56% (50-73); 10^{-6}M, 56% (34-82), p=0.607. Chloride secretion was: 10^{-1}M, 8.5mV (6.9-15.3); 10^{-3}M, 24.3mV (18.8-37.5); 10^{-6}M, 17.3mV (11.1-33.4), p=0.115.

Discussion: In healthy volunteers, nasal perfusion of metformin over 20-30 minutes did not inhibit sodium absorption across nasal epithelium, even at high concentrations. Metformin 10^{-1}M did significantly inhibit chloride secretion and this effect appeared greater than at lower metformin concentrations. In vitro, metformin treatment for at least 16 hours inhibited ENaC and increased ASL height (Myerburg et al, 2010). Further studies are now required to determine whether longer duration treatment with metformin inhibits sodium absorption across human airway epithelium.