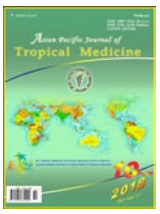

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TRPM8 is overexpressed in the respiratory tract of steroid−naive asthma patients

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ABSTRACT **Background:** TRPM8 is a member of TRP channels family known for its sensitivity to cool temperature, increased osmotic pressure, particulate matter, cigarette smoke and products of oxidative stress. This cation channel is widely expressed in the respiratory tract including airway epithelium and vagal nerve endings where it can mediate inflammatory and secretory responses. Previous studies have reported the increased expression of TRPM8 in the respiratory tract of COPD patients. **Objective:** To investigate TRPM8 expression in nasal epithelium and induced sputum of asthma patients and to estimate its relation to airway hyperresponsiveness induced by cold air. **Methods**: The study enrolled 43 subjects with mean age of (39.8±1.76) years including 35 patients with mild-to-moderate asthma and 8 patients with chronic bronchitis. Among the asthma patients 43% were steroid-naïve. Lung function was measured by standard spirometry before and after bronchoprovocation challenge with 3 min isocapnic cold air (-20 ℃) hyperventilation. Cold air hyperresponsiveness was diagnosed in case of FEV1 falling by 10% from baseline. TRPM8 expression was measured by indirect flow cytometry in nasal brushings and induced sputum. Nasal epithelium cells were gated after exclusion of dead cells and staining with anti-cytokeratin 19 antibodies. Induced sputum was processed with dithiothreitol, filtered and stained for CD45 and cell viability. Extracellular expression of TRPM8 was detected by staining with primary unconjugated anti-TRPM8 antibodies (Alomone Labs) and secondary antibodies labeled with Alexa Fluor 488 (Abcam). Expression level was calculated as normalized median fluorescence intensity (nMFI) and percent of positively stained cells (%Pos). The data are presented as median, lower and upper quartiles (Me (Q1; Q3)). **Results:** TRPM8 protein was detected on the epithelial cells and sputum macrophages. The expression levels of TRPM8 were significantly correlated in these cells (nMFI R=0.41, P=0.04; %Pos R=0.53, P=0.008). Expression of TRPM8 was increased both in nasal epithelium and macrophages of steroid-naïve asthma patients as compared to the patients receiving maintenance therapy or patients with chronic bronchitis. nMFI values for macrophages were 2.1 (1.95; 2.79), 1.3 (1.10; 1.91) and 1.2 (1.06; 1.35), respectively (P=0.001). %Pos values for macrophages were 38.5 (13.1; 51.1)%, 11.6 (2.55; 20.1)% and 8.0 (3.20; 9.20)%, respectively (P=0.01). nMFI and %Pos values for the epithelium kept the same trend but the differences were mostly insignificant. In addition, we found a correlation between FEV1 in response to cold air hyperventilation challenge and TRPM8 expression (macrophages %Pos R=-0.43, P=0.02; epithelium %Pos R=-0.43, P=0.08). Cold airway hyperresponsiveness was accompanied by higher TRPM8 expression on macrophages (21.6 (17.1; 40.7)% *vs.* 11.6 (7.45; 16.55)%, P=0.03) and nasal epithelium (4.2 (3.30; 5.40)% *vs.* 2.8 (1.10; 4.30)%, P=0.2). Cold airway hyperresponsiveness was not affected by maintenance therapy in our patients. **Conclusions:** TRPM8 is overexpressed in steroid-naïve asthma patients as well as in asthma patients with cold airway hyperresponsiveness and may be implicated in asthma pathogenesis. The utility of TRPM8 as a diagnostic biomarker or therapeutic target in chronic obstructive airway diseases is of great interest.

Keywords: TRPM8; Expression; Asthma; Nasal epithelium; Induced sputum; Cold airway hyperresponsiveness
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