Characterization of Transient Receptor Potential Vanilloid-1 (TRPV1) Variant Activation by Coal Fly Ash Particles and Associations with Asthma

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Asthma is a common airway inflammatory disease. Allergens, air pollution, and various other environmental pollutants are associated with the development and acute exacerbation of asthma. Transient receptor potential vanilloid-1 (TRPV1) is activated by numerous environmental particulate materials including a representative combustion-generated particulate material, coal fly ash. Several studies have examined roles for TRPV1 in asthma and have shown that TRPV1 can be expressed at higher levels in epithelial cells and neurons in the bronchi of asthmatics with both mild and refractory (steroid-insensitive) asthma, as well as in neurons of individuals with chronic cough, and in peripheral blood cells of children with asthma. We hypothesized that polymorphic variants of TRPV1 would be uniquely responsive to insoluble coal fly ash compared to the prototypical soluble agonist capsaicin. Furthermore, these changes would manifest as differences in lung cell responses to these agonists and perhaps correlate with changes in asthma symptom severity and control. The TRPV1 I315M and T469I variants were inherently more responsive to capsaicin and coal fly ash. The I585V variant was less responsive to coal fly ash, due to reduced protein expression and an apparent role for I585 in activation by insoluble particles. The I315M and I585V variants (heterozygotes) were associated with worse asthma symptom control. The effect of I585V on asthma was surprising given that it was less responsive to a model environmental particle pollutant in functional assays and expressed at lower levels in lung cells. However, in human lung epithelial cells from donors heterozygous for TRPV1 I585V TRPA1 was expressed at higher levels. TRPA1 is typically not expressed by lung epithelial cells and is activated by combustion-generated environmental particles that affect asthma, including diesel exhaust particles, wood smoke, and cigarette smoke. This study suggests I315, T469, and I585 are involved in TRPV1 activation by particles and changes in the expression of TRPA1 by epithelial cells due to I585V expression could contribute to variations in asthma symptom severity and control. Support: ES017431, HD 060559, and the University Of Utah Department of Pediatrics.

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