ORIGINAL ARTICLE

Airway and serum adipokines after allergen and diesel exposure in a controlled human crossover study of atopic adults

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Adipokines are mediators released from adipose tissue. These proteins are regarded as active elements of systemic and pulmonary inflammation, whose dysregulation can alter an individual's risk of developing allergic lung diseases. Despite this knowledge, adipokine responses to inhaled stimuli are poorly understood. We sought to measure serum and lung adiponectin, leptin, and resistin in an atopic adult study population following exposure to allergen and diesel exhaust (DE). Two types of lung samples including bronchoalveolar lavage (BAL) and bronchial wash (BW), and a time course of serum samples, were collected from the 18 subjects who participated in the randomized, double-blinded controlled human study. The two crossover exposure triads in this study were inhaled DE and filtered air each followed by instilled allergen or saline. Serum and lung adipokine responses to these exposures were quantified using enzyme-linked immunosorbent assay. Allergen significantly increased adiponectin and leptin in BAL, and adiponectin in the BW 48 hours after exposure. Serum leptin and resistin responses were not differentially affected by exposure, but varied over time. Coexposure with DE and allergen revealed significant correlations between the adiponectin/leptin ratio and FEV_1 changes and airway responsiveness measures. Changes in lung and serum adipokines in response to allergen exposure were identified in the context of a controlled exposure study. Coexposure identified a potentially protective role of adiponectin in the lung. This response was not observed in those with baseline airway hyper-responsiveness, or after allergen exposure alone. The clinical relevance of this potentially adaptive adipokine pattern warrants further study. (Translational Research 2016;■:1–12)

Abbreviations: A/L = adiponectin (ng)/leptin (ng); APEL = air pollution exposure laboratory; BAL = bronchoalveolar lavage; BW = bronchial wash; BMI = body mass index, kg/m^2; DE = diesel exhaust; DEA = diesel exhaust and allergen; DES = diesel exhaust and saline; DRS = dose-response slope; ELISA = enzyme-linked immunosorbent assay; FA = filtered air; FAS = filtered

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air and saline; FAA = filtered air and allergen; FEV_1 = forced expiratory volume in first second of exhalation, L; mL = milliliter; PC_{20} = methacholine concentration that causes a 20% reduction in FEV_1; PM = particulate matter; $PM_{2.5}$ = particulate matter less than 2.5 microns in aerodynamic diameter; RML = right middle lobe; SAC = segmental allergen challenge

AT A GLANCE COMMENTARY

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Background

Adipokines are inflammatory mediators that are dysregulated in allergic lung disease. They may have a causal role in asthma. Further, relative levels of anti-inflammatory (adiponectin) and proinflammatory (leptin) adipokines appear to be important, and has shown to be a predictor of asthma status and severity.

Translational Significance

Co-exposure identified a potentially protective role of adiponectin in the lung in those with normal airway responsiveness, but not in those with baseline airway hyper-responsiveness. The adipokine response in normal subjects may protect against common co-exposures; those not mounting such a response may be at risk for inflammatory lung disease.

INTRODUCTION

Adipokines are diverse inflammatory mediators released primarily from the adipose tissue.[1-3] These mediators impact inflammation both systemically, and in tissues such as the airways.[4,5] The most commonly studied adipokines include adiponectin, leptin, and resistin. Leptin[6-10] and resistin[11-13] are thought to be proinflammatory, whereas adiponectin is typically anti-inflammatory.[14-16] The relative level of anti- and proinflammatory adipokines, the adiponectin-to-leptin (A/L) ratio, also appears to be important. Adipokine dysregulation in inflammatory lung diseases, including asthma, has been noted. In particular, adiponectin and leptin, and the A/L ratio,[5,17] seem to be predictive of asthma status and severity, and are acutely altered in the serum during asthma exacerbations. Several investigators hypothesize that adipokines have a causal role in asthma,[18,19] although the mechanisms by which they contribute remain unclear.

Allergen exposure and sensitization is a known risk factor for asthma development.[20] Animal models suggest that adipokine levels change in serum and bronchoalveolar (BAL) 24 or 48 hours following allergen exposure, causing altered systemic and pulmonary inflammation and airway hyperresponsiveness.[21-23] Most studies of adipokine responses in humans have been limited to systemic measures of adipokine responses. They have generally not measured adipokine changes in the lung, the site of primary contact with allergen exposures,[3] and have therefore not examined the dynamic and complex interplay between systemic and pulmonary adipokine sources. One exception is a recent study in subjects with red cedar asthma that showed increased sputum adiponectin levels 6 hours after inhaled plicatic acid exposure.[24] Another notable limitation is that exposure to allergen in the environment occurs in combination with other exposures, like particulate pollution, that acts to enhance the allergenicity of exposure.[25] The effects of this environmentally relevant coexposure on adipokine responses are also unknown.

To address the aforementioned gap, we aimed to characterize serum and lung adipokine responses following diesel exhaust (DE) and allergen coexposure in atopic participants. We hypothesized that segmental allergen challenge (SAC) would alter BAL, bronchial wash (BW), and serum concentrations of adiponectin, leptin, the A/L ratio, and resistin and that a 2-hour inhalation of DE at 300 μg $PM_{2.5}/m^3$ before allergen would enhance the allergenicity of the exposure,[26,27] and therefore cause a larger adipokine response.

METHODS

Human ethics and consent. In accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki), all participants provided written informed consent before participation. This study was approved by the ethical review boards at the Vancouver Coastal Health Research Institute and the University of British Columbia. The study was registered at clinicaltrials.gov (trial no. NCT01792232).

Subject recruitment. Adults between the ages of 19–49 were recruited using both referral of clinical patients, and local advertising. Primary screening excluded participants meeting any of the following criteria: (1) pregnant/breastfeeding, (2) use of inhaled corticosteroids, (3) regular use of bronchodilator medication, (4) unstable asthma symptoms, (5) any use of vitamins A, C, E, or other antioxidant supplements, (6) comorbid conditions judged by the investigators to increase risk of