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Glucagon-like peptide 1: A potential anti-inflammatory pathway in obesity-related asthma

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ABSTRACT

Alterations in arginine metabolism and accelerated formation of advanced glycation end-products (AGEs), crucial mechanisms in obesity-related asthma, can be modulated by glucagon-like peptide 1 (GLP-1). L-arginine dysregulation in obesity promotes inflammation and bronchoconstriction. Prolonged hyperglycemia, dyslipidemia, and oxidative stress leads to production of AGEs, that bind to their receptor (RAGE) further potentiating inflammation. By binding to its widely distributed receptor, GLP-1 blunts the effects of RAGE activation and arginine dysregulation. The GLP-1 pathway, while comprehensively studied in the endocrine and cardiovascular literature, is under-recognized in pulmonary research. Insights into GLP-1 and the lung may lead to novel treatments for obesity-related asthma.

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1. Obesity-related asthma

While traditionally considered to be an allergic disease of reversible airway obstruction, asthma is more aptly described as a syndrome, presenting with many different subtypes. Characterization of asthma phenotypes continues to be an active area of research, but some categories include age of onset (childhood or adult), allergic (T-helper type 2 cell inflammatory responses, Th2-high), or non-allergic (Th2-low). Th2-high asthma is generally responsive to the accepted treatment paradigms of corticosteroids, bronchodilators, and allergy control.

However, asthma afflicts over 20 million people in the United States and approximately 50% have uncontrolled disease, which is associated with a decreased quality of life and increased health care system (Centers for Disease Control, 2017). While the underlying pathobiology is diverse and complicated, the most advanced asthma therapies are directed solely towards Th2-high asthma, with biologics that inhibit immunoglobulin E or interleukin-5. These therapies are expensive and may be ineffective for Th2-low asthma. Although there are many non-pharmacologic factors that contribute to uncontrolled asthma, novel therapies are urgently needed.

Abbreviations: AGEs, Advanced glycation end products; ADMA, Asymmetric dimethylarginine; cAMP, Cyclic adenosine monophosphate; DPP-4, Dipeptidyl peptidase 4; GLP-1, Glucagon-like peptide 1; GLP-1R, Glucagon-like peptide 1 receptor; HMGB-1, High mobility group box 1 protein; IL, Interleukin; MAPK, Mitogen-activated protein kinase; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NO, Nitric oxide; NOS, Nitric oxide synthase; PKA, Protein kinase A; RAGE, Receptor for advanced glycation end products; Th1, T-helper type 1 cell; Th2, T-helper type 2 cell; TNF-α, Tumor necrosis factor alpha.

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In the United States, approximately 35% of all adults are obese, and 39% of adults with asthma are obese (Centers for Disease Control, 2017; Ogden, Carroll, Fryar, & Flegal, 2015). Obesity and metabolic syndrome are associated with an increased risk of coincident asthma and may represent distinct asthma phenotypes (Brumpton et al., 2013; Camargo, Weiss, Zhang, Willett, & Speizer, 1999). Some have traditional Th2-high asthma, but others have an increasingly recognized Th2-low asthma that tends to be more common in women, later in onset, and difficult to treat (Dixon & Poynter, 2016).

Despite strong epidemiologic data linking obesity and asthma, the underlying mechanisms of this relationship are complicated and incompletely understood. Suggested links include chronic inflammation, mitochondrial dysfunction, Th17-induced neutrophilia, macrophage dysregulation, hormonal changes, lipid metabolism, insulin resistance, and body mechanics (Baffi et al., 2016; Chesne et al., 2014; Shore & Cho, 2016). Other well-described abnormalities in obesity and metabolic syndrome, accelerated formation of advanced glycation end products (AGEs) and alterations in arginine metabolism may also play a crucial role in asthma pathogenesis and may be modulated by the anti-inflammatory incretin, GLP-1 (Fig. 1) (Holguin, 2013; Milutinovic, Alcorn, Englert, Crum, & Oury, 2012; Ojima et al., 2013; Singh et al., 2015; Uribarri et al., 2015).

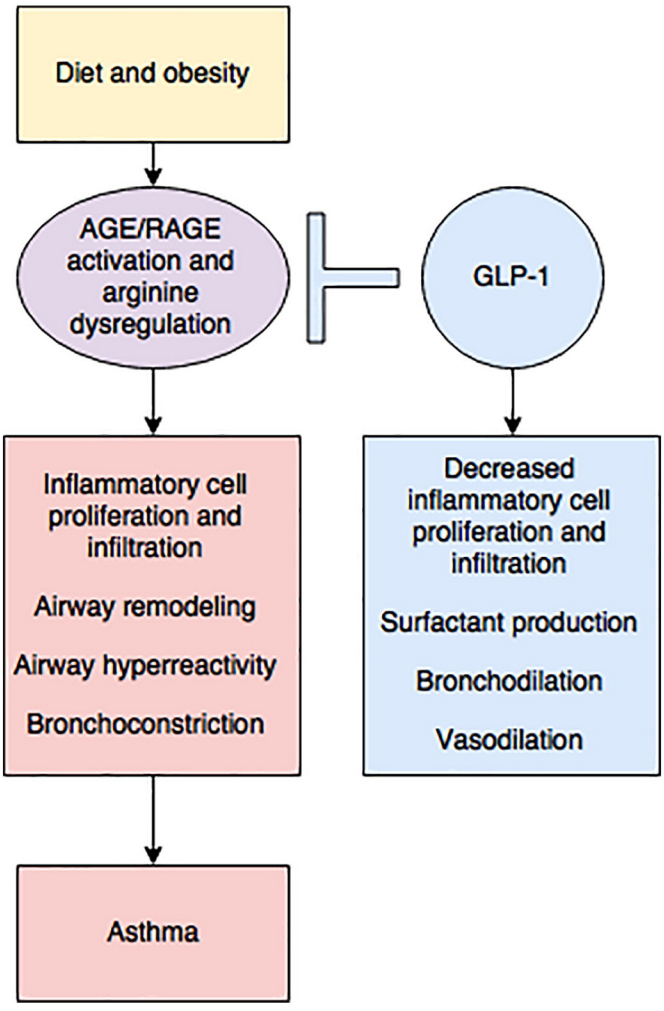

Fig. 1. Diet and obesity may lead to dysregulated arginine metabolism and increase the production of advanced glycation end products (AGE) and subsequent activation of their receptor (RAGE), contributing to inflammation and asthma. The GLP-1 pathway may be critical to attenuating this inflammation.

2. Advanced glycation end-products and their receptor

AGEs are highly reactive, non-enzymatically glycated proteins or lipids implicated in the modulation of inflammatory responses. All proteins have some amount of AGE modification, but AGE formation is typically slow under normal healthy conditions (Kellow & Coughlan, 2015). Persistent hyperglycemia, dyslipidemia, and oxidative stress may accelerate AGE production. AGEs can also be consumed from foods prepared with intense heat (such as baking or frying). Serum AGEs are markers of insulin resistance and inflammation, and elevated levels may distinguish metabolic syndrome from obesity (Uribarri et al., 2015).

Interactions between AGEs and their receptor (RAGE) generate oxidative stress and perpetuate inflammatory, thrombogenic, and fibrotic reactions (Yamagishi, Nakamura, Suematsu, Kaseda, & Matsui, 2015). RAGE is a type of immunoglobulin cell surface marker, expressed constitutively and ubiquitously at low levels (Buckley & Ehrhardt, 2010; Demling et al., 2006). It can bind to a diverse number of ligands in addition to AGEs, such as high mobility group box 1 protein (HMGB1), amyloid fibrils, and S100 proteins. Upregulation of RAGE or its ligands results in a pro-inflammatory cascade activating NF-κB, TNF-α, IL-1β and IL-8, and is seen in diseases ranging from Alzheimer's to atherosclerosis (Bierhaus et al., 2005; Tobon-Velasco, Cuevas, & Torres-Ramos, 2014). Yet, there are also soluble isoforms of RAGE in the serum, whose roles are incompletely understood, but may act to scavenge RAGE ligands before they activate the membrane-bound receptor.

Lung tissues have high levels of RAGE expression. Located on type I alveolar cells, it may promote spreading of adherent cells on collagen IV, helping to ensure effective gas exchange. However, RAGE overactivation may be deleterious and central in asthma pathogenesis. Asthmatics may have greater levels of neutrophils, HMGB1, and RAGE in their sputum. Moreover, HMGB1 seems to correlate with asthma severity and might serve as a novel biomarker of disease (Watanabe et al., 2011; Zhou et al., 2012).

Experimentally, RAGE knockout mice exhibit decreases in airway hypersensitivity, remodeling, and both Th1 and Th2 cytokines (Akirav et al., 2014; Milutinovic et al., 2012; Taniguchi et al., 2015). Taniguchi et al. found that RAGE on lung structural cells but not on hematopoietic cells resulted in allergic inflammation, while RAGE on hematopoietic cells and absent in the lung showed reduced inflammation. Interestingly, the absence of RAGE on lung structural cells also resulted in increased levels of IL-33 and enhanced innate airway hyperresponsiveness (Taniguchi et al., 2015). The mechanisms behind this are unclear, but allude to its complex role in regulating airway inflammatory responses.

Undoubtedly, these experimental links provide clues as to why AGE-RAGE inflammation in obesity and diabetes could potentiate asthma. This may then be directly attenuated by GLP-1, which reduces RAGE expression, downstream RAGE signaling, and inflammatory chemokines (Ojima et al., 2013; Yamagishi et al., 2015). These effects were seen in experiments with human kidney tubular cells and a rat model of diabetes. Furthermore, co-existing with RAGE-mediated inflammation, dysregulated arginine metabolism may be another important pathway that can be addressed through GLP-1 (Ojima et al., 2013).

3. Arginine metabolism

L-Arginine is a substrate in a number of diverse metabolic pathways, including the synthesis of nitric oxide (NO), and it stimulates the production of GLP-1. Arginine converts to nitric oxide primarily via nitric oxide synthase (NOS), which can create both beneficial and inflammatory reactive species of nitric oxide. Arginine can also be hydrolyzed through arginase, which catalyzes the formation of L-ornithine, urea, and L-proline. Furthermore, it can undergo methylation and generate asymmetric dimethylarginine (ADMA), an endogenous NOS inhibitor. Dysregulation of arginine metabolism occurs in obesity, metabolic syndrome, and asthma,

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