Glucagon Like Peptide 1 Attenuates Airway Hyperresponsiveness in a Mouse Model of Obese Allergic Asthma

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Rationale. Asthma is a chronic inflammatory disease affecting hundreds of millions of people worldwide. Obesity has been shown to increase airway inflammation and exacerbate asthma. The neuropeptide glucagon like peptide1 (GLP-1) has been shown to reduce weight and improve glucose tolerance in mouse models of obesity. It also has several extrapancreatic effects, including anti-inflammatory and anti-fibrotic properties. GLP-1 has been measured in the lung, and recent studies have suggested that it may play a role in asthma, as GLP-1 analogs and inhibitors of dipeptidyl peptidase-4 (which degrades GLP-1) have been reported to improve asthma control and reduce exacerbations in patients with asthma. We hypothesized that treatment with GLP-1 would reduce airway inflammation, hyperresponsiveness (AHR) and fibrosis in mouse models of obese allergic asthma. To test our hypothesis, we tested a novel GLP-1 analog where GLP-1 is fused to a thermally sensitive Elastin Like Polymer (ELP) that is soluble at room temperature, but forms a depot upon subcutaneous injection at body temperature. This GLP-1 analog was previously shown to be effective in reducing blood glucose levels in mice for up to 5 days, 120 times longer than an injection of the native peptide. Methods. 6wk old C57BL/6J male mice were fed high fat diet for 8wk. Mice were treated with a weekly subcutaneous injection of GLP-1-ELP, ELP control, or saline control (200µM, 3.5µl/g, s.c.) and sensitized with 100µg (total protein) i.p. house dust mite extract (HDM) or saline on day7 and then challenged with 100µg i.t. HDM (Lot #326779) or saline 3x/wk for 5wk starting on day21. Airway hyperresponsiveness to methacholine was determined 48h following the final challenge. Bronchoalveolar lavage fluid (BALF) and fixed lung tissue were analyzed for inflammatory cells, cytokines/chemokines, mucus production, and collagen deposition. Airway fibrosis was assessed using Masson’s trichrome staining. Results. GLP-1-ELP significantly reduced weight gain in HFD mice and improved glucose control in HFD mice compared to controls (p<0.05). Treatment with GLP-1-ELP significantly attenuated AHR (Rrs) and lung stiffness (Ers) in mice after chronic HDM exposure (p<0.05). At the time point checked, GLP-1-ELP appeared to have no effect on inflammation, cytokine levels, airway fibrosis or mucus production after chronic HDM exposure. Conclusions. These data demonstrate potential for GLP-1 as a novel therapeutic for the control of AHR in obese asthma. Further studies including additional time points and assessing mechanism of action are needed.

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