



Evaluating the glucagon-like peptide-1 receptor in managing asthma

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Purpose of review

The aim of this study was to discuss the role of glucagon-like peptide-1 (GLP-1) receptor signalling in reducing lung inflammation and potential use for GLP-1 receptor agonists (GLP-1RAs) in management of asthma.

Recent findings

Although GLP-1RA are currently used for the treatment of type 2 diabetes (T2D) and weight loss in obesity, there is much interest in expanding the indications for use in other diseases, including inflammatory pulmonary disease. In animal models of both acute and chronic pulmonary disease, use of GLP-1RA reduces airway inflammation, obstruction and fibrosis. In particular, GLP-1 receptor (GLP-1R) signalling seems to inhibit allergen-induced type 2 inflammation, making it an attractive agent for asthma. Results are especially promising in disease processes with disturbed metabolic regulation, such as T2D or metabolic syndrome. Retrospective clinical studies demonstrate promising evidence for the use of GLP-1RAs in comorbid diabetes and asthma, although prospective human studies are limited.

Summary

Here, we discuss the biology of GLP-1 and GLP-1R signalling, review the preclinical and mechanistic evidence for how GLP-1R signalling may reduce pulmonary inflammation, and summarize recent and upcoming clinical studies. Ultimately, targeting GLP-1R signalling may represent a novel approach for asthma therapy that is glucocorticoid sparing and possibly disease modifying.

Keywords

airway inflammation, asthma, glucagon-like peptide-1, interleukin-33, type 2 inflammation

INTRODUCTION

As one of the most prevalent chronic illnesses, asthma continues to have a significant global burden of disease, affecting over 25 million people in the USA and as many as 330 million people worldwide [1]. Unfortunately, accessible treatment options such as glucocorticoids and beta-adrenergic agonists – options that may be suboptimal for an increasingly recognized subset of patients with ‘type 2 inflammation-low’ asthma – remain limited. Newer biologic agents are promising, particularly in refractory asthma, but these treatments remain cost-prohibitive for most patients. Thus, there is a need for novel agents that can target different pathways driving airway inflammation seen in asthma.

Glucagon-like peptide-1 (GLP-1) receptor signalling represents a promising target for modulating airway inflammation. Although GLP-1 receptor (GLP-1R) agonists are currently approved for type 2 diabetes mellitus (T2D) and chronic weight management in obesity, preclinical studies have

demonstrated potential multisystemic anti-inflammatory effects with benefits that extend beyond weight loss and controlling hyperglycaemia. Administration of exogenous GLP-1R agonists (GLP-1RAs) in animal models is protective in models of pulmonary inflammation [2,3,4^a,5]. Recent retrospective reviews in humans with comorbid T2D and asthma have echoed similar findings [6^a,7^a,8]. Thus, targeting the GLP-1R remains enticing for the management of asthma, as GLP-1RAs are widely

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KEY POINTS

- GLP-1RAs are currently approved for use in type 2 diabetes and weight loss; however, preclinical evidence suggests broader anti-inflammatory effects and applications for use.
- GLP-1R signalling may inhibit the innate allergic immune response by decreasing lung eosinophilia, ILC2 proliferation and secretion of type 2 inflammatory cytokines.
- In the United States, most adults with severe asthma are obese, and those with obese asthma are more likely to exhibit a Th2-low, or 'neutrophilic', phenotype. In a mouse model of obese allergic disease, GLP-1RA decreases airway neutrophilia, suggesting a unique mechanism for anti-inflammatory effect that may have broad therapeutic potential across various asthma phenotypes.
- GLP-1R signalling remains an attractive target for the management of asthma as an anti-inflammatory agent that is glucocorticoid-sparing and may even be disease modifying.

available and already highly effective, multipurpose drugs for diabetes and obesity, conditions that are often comorbid with asthma.

Biology of glucagon-like peptide-1 and current uses

Derived from the posttranslational modification of proglucagon peptide, GLP-1 is a neuroendocrine peptide hormone known as an incretin. It is secreted from intestinal L-cells and neurons within the nucleus of the solitary tract in the brainstem in response to ingestion of food [9]. Incretin hormones lower blood glucose by stimulating endogenous insulin secretion. GLP-1 also helps maintain euglycaemia by suppressing glucagon secretion and slowing gastric emptying, which reduces food intake, moderates postprandial hyperglycaemia and normalizes fasting hyperglycaemia.

GLP-1 is the only known ligand for GLP-1R, a Gs-protein coupled receptor (GPCR), which can activate a multitude of downstream pathways, including cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA), cAMP/guanine-nucleotide exchange factor and phosphatidylinositol-3 kinase/Protein Kinase C. Of note, β_2 adrenergic agonists, prostaglandin E_2 and phosphodiesterase inhibitors cause airway smooth muscle cell relaxation via activation of cAMP [10]. It has been challenging to characterize organ and cell-type specific expression of GLP-1R, as there are some incongruities between human and murine

GLP-1R expression. One study found human GLP-1R to be expressed in the pulmonary vasculature, airway smooth muscle cells and epithelial cells, and type II alveolar cells [11]. A different study only found GLP-1R to be expressed in the arterial and arteriolar smooth muscle cells. In contrast, murine GLP-1R was found to be ubiquitously expressed throughout the lung [12]. Unfortunately, commercially available anti-GLP-1R antibodies have been relatively nonspecific, thereby making it hard to characterize the true expression of GLP-1R by common techniques.

Use of GLP-1RAs for T2D has been exciting as they are robust antidiabetic agents with minimal hypoglycaemic risk. Currently, five GLP-1RAs are Food and Drug Administration (FDA)- and National Institute for Health and Care Excellence-approved for prescription-use in the USA and the UK, respectively (Table 1). Furthermore, they can be effective agents to augment weight loss, which is key in comorbid obesity and metabolic syndrome.

Role for glucagon-like peptide-1R signalling beyond glycaemic control

GLP-1R is expressed abundantly in numerous organs aside from the pancreas and gastrointestinal tract, including the heart, lung, brain and kidney [13]. Although GLP-1R signalling in satiety and glycaemic control is well described, the role of GLP-1R signalling in other organ systems remains unclear. One area of particular interest is in the lung, where GLP-1R is expressed at significantly higher levels than in other organs [14]. In animal models of acute and chronic pulmonary disease processes, liraglutide reduced lipopolysaccharide (LPS)-induced acute lung injury (ALI), ovalbumin (OVA)-induced chronic airway inflammation and bleomycin-induced pulmonary fibrosis [2,15,16].

Glucagon-like peptide-1R signalling inhibits allergen-induced inflammation

Asthma is classically described as an 'allergic' disease marked by type 2 inflammation. Key cell types include mast cells, eosinophils, basophils, $CD4^+$

Table 1. Currently available GLP-1R agonists

Dulaglutide
Exenatide
Liraglutide ^a
Lixisenatide
Semaglutide ^{a,b}

^aFDA-approved for indication of chronic weight management in obesity.

^bOnly GLP-1RA currently also available in oral form; all others are subcutaneous injections.

T-helper type 2 (Th2) cells and group 2 innate lymphoid cells (ILC2s). Hallmarks of this chronic lung disease include airway hyperresponsiveness that results in bronchospasm and mucus production. In asthma, compared with other types of obstructive airway disease, obstruction is reversible, but chronic inflammation can result in airway remodelling (smooth muscle hypertrophy, mucus metaplasia, collagen deposition) that may be irreversible. In response to exposure to allergic antigens, airway epithelial cells and pulmonary macrophages secrete interleukin-33 (IL-33) that activates Th2 cells, ILC2, mast cells and basophils [17,18]. These cells subsequently secrete a variety of type 2 inflammatory cytokines including IL-4, IL-5, IL-9 and IL-13, which act on goblet cells and smooth muscle cells to amplify the allergic response in immune cells and induce airway remodelling [19].

In a mouse model for asthma, treatment with liraglutide decreased lung tissue IL-33, eosinophilia and ILC2 proliferation 1 h after challenge with *Alternaria alternata*, a fungal aeroallergen. In addition, ILC2 secretion of type 2 inflammatory cytokines, IL-5 and IL-13, was decreased, suggesting that GLP-1R signalling may inhibit the innate allergic immune response in the lung [20].

Glucagon-like peptide-1R signalling may mitigate exacerbations of lung disease by relieving airway obstruction

As mentioned previously, there are several downstream pathways GLP-1R, a GPCR, may signal through. In one ex-vivo study, exendin-4, a GLP-1RA also known as exenatide, mitigated bronchial hyperresponsiveness in human airway cells stimulated by passive allergen sensitization and a high-glucose environment. Treatment with cAMP-dependent PKA inhibitor, KT5720, abrogated the protective effect of exendin-4; however, subsequent retreatment with exendin-4 resulted in overexpression of adenylyl cyclase and restoration of depleted cAMP [11]. In a mouse model of asthma, exenatide as well as liraglutide decreased airway mucus hypersecretion and nuclear factor- κ B in response to OVA challenge, possibly via PKA-dependent mechanism [2]. In another mouse study, a decrease in cAMP within dendritic cells was associated with increased dendritic cell-mediated Th2 polarization with a prominent allergic phenotype. cAMP stimulation inhibited this Th2-skewed differentiation [21].

Treatment with GLP-1RA may improve the mechanics of airflow even in individuals without lung disease, suggesting a pulmonary-protective role beyond decrease in inflammation. One study compared spirometry data in individuals with diabetes without lung disease. Those individuals on

GLP-1RAs and metformin had relatively higher average forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) compared with those on metformin alone or metformin and insulin [22]. These findings were robust after accounting for change in hemoglobin A1c (HbA1c). Weight loss on treatment, which is known to improve lung function in asthma, was not accounted for in this small cohort study. The exact mechanism of benefit of GLP-1RA use on lung function is unknown.

Despite the improvement seen in certain measures of lung function, it is unclear whether GLP-1RA improve lung compliance. In mouse models of ALI, GLP-1RAs seem to protect against LPS-induced reduction in surfactant [23–25]. However, other studies have reported conflicting results [14,20,26,27]. The role of endogenous GLP-1 signalling in the lung is likely multifactorial and complex, particularly in a diseased state, and may depend on the mechanism of pulmonary injury. The response to GLP-1RA may in fact be disease-specific [3].

Glucagon-like peptide-1RA: an attractive agent for comorbid obese asthma?

Sixty percent of adults with severe asthma in the United States are obese [28]. The association between obesity, metabolic syndrome and asthma remains unclear. One possible connection may be related to an altered inflammatory response. Previously defined in terms of severity and frequency of exacerbations, asthma is now more precisely characterized as a clinically heterogeneous disease with multiple phenotypes. The most well described phenotypes are ‘type 2 inflammation high’ (Th2-high) and ‘type 2 inflammation low’ (Th2-low). Th2-high asthma, also known as ‘eosinophilic asthma,’ is thought to have more of a classic, steroid-responsive, phenotype, while Th2-low asthma, or ‘neutrophilic asthma,’ is generally more refractory to steroids [29,30]. Adults with obese asthma are more likely to exhibit the Th2-low phenotype than their nonobese counterparts [31].

One study using TALLYHO mice, a polygenic mouse model of obesity, demonstrated a promising role for GLP-1RAs in these comorbid conditions (Fig. 1). Compared with lean mice, obese TALLYHO mice had greater *Alternaria*-induced airway neutrophilia, ICAM-1 expression on lung epithelial cells, and lung tissue expression of IL-5, IL-13, CCL11, CXCL1 and CXCL5. *Alternaria* challenge, compared with isotonic saline challenge, also increased bronchoalveolar lavage fluid (BALF) IL-33 in both obese and lean strains, though differences in levels between the strains were not significant. Administration of GLP-1RA significantly decreased all the

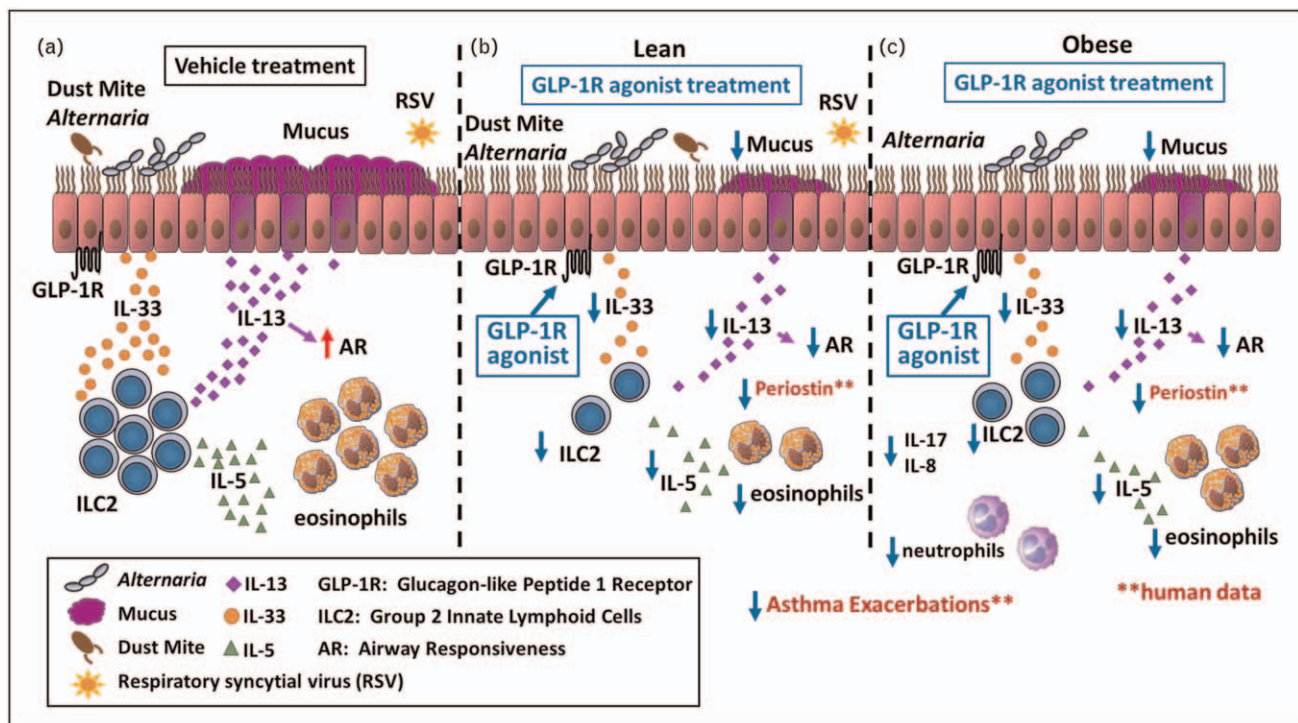


FIGURE 1. In both lean and obese mouse models of allergen- and viral-induced airway inflammation, GLP-1RA treatment reduces lung IL-33, ILC2 recruitment, eosinophilic and neutrophilic inflammation, and type 2 and non-type 2 cytokine production. (a) Alternaria extract, dust mite, and RSV-challenged mice develop increased airway inflammation. (b) Pretreatment with a GLP-1RA in lean mice reduces type 2 airway inflammation. (c) Treatment with GLP-1RA in obese mice reduces type 2 and non-type 2 airway inflammation. **In humans, treatment with GLP-1RA lowers periostin and reduces asthma exacerbation risk.

aforementioned allergen-induced endpoints in TAL-YHO mice, including reduction of neutrophilia. Interestingly, reduction of neutrophilia was not seen with inhibition of either thymic stromal lymphopoietin (TSLP) or ST2, both of which are currently being investigated as targets for asthma therapy [4^o]. In another mouse model of obesity, liraglutide reduced LPS-induced ALI by downregulating NLRP3 inflammasome and IL-1 β [32]. Similar findings were demonstrated in a lean mouse model of asthma [23]. These studies suggest that GLP-1R signalling may act through a unique, nonsteroidal anti-inflammatory pathway that may have broad therapeutic potential across various asthma phenotypes.

In addition to inhibition of the inflammasome, several other pathways have been postulated as potential targets of GLP-1R signalling. It is thought that arginine metabolism and nitric oxide homeostasis is dysregulated in obesity [33]. One possible mechanism of GLP-1R signalling is that GLP-1RA may inhibit asymmetric dimethylarginine, an arginine gene product that is a competitive inhibitor nitric oxide synthase [34].

Glucagon-like peptide-1RA in human studies

In a pilot observational cohort study, nine non-smoker patients with asthma – seven of whom remained on liraglutide, two of whom discontinued liraglutide after 8 weeks due to intolerance – were observed over a period of one calendar year. One of the two patients who discontinued liraglutide experienced an asthma exacerbation shortly after discontinuation of the GLP-1RA, whereas none of the seven patients on liraglutide had clinical deterioration in their asthma [35]. Although it was difficult to draw any definitive conclusions due to the small number of patients in this uncontrolled cohort study, there remains avid interest in investigating the role of GLP-1RA in those with comorbid diabetes and asthma.

Subsequently, multiple large retrospective human studies have demonstrated promise of GLP-1RA in patients with asthma. One retrospective cohort study compared pulmonary outcomes in patients with comorbid T2D and chronic lower respiratory disease while on GLP-1RAs vs. dipeptidyl peptidase IV (DPP-IV) inhibitors as a second-line

antidiabetic agent [6[¶]]. As a primary outcome, this study found that patients on GLP-1RAs had a lower risk of hospitalization compared to those on DPP-IV inhibitors [10.7/1000 person years vs. 20.3/1000 person years, respectively; hazard ratio 0.52, 95% confidence interval (95% CI) 0.32–0.85]. They also had a lower risk of exacerbations, 13/1000 person years fewer. Of note, CIs were wider when stratified for specific diseases, including asthma, as there was a small overall number of events. A meta-analysis that included patients from multiple large clinical trials investigating the potential cardiac benefits of GLP-1RAs found a trend towards decreased pulmonary events in those on GLP-1RAs compared with other antidiabetic agents [8]. Again, the relatively low incidence of certain pulmonary disorders and respiratory adverse events lowered statistical power.

A recent retrospective cohort study of patients with comorbid asthma and diabetes revealed lower numbers of asthma exacerbations in patients on GLP-1RAs compared with other antidiabetic agents [7^{¶¶}]. Using electronic health record data, asthma exacerbations, defined as a systemic glucocorticoid prescription, were assessed between asthmatic individuals with T2D initiating either a GLP-1RA or other T2D agent. Using a Poisson regression model, patients initiating GLP-1RAs experienced substantially fewer asthma exacerbation events within 6 months of treatment initiation compared with patients initiating long-acting insulins, SGLT-2 inhibitors, sulfonylureas and DPP-IV inhibitors. These findings held when baseline and change in BMI and HbA1c were included as covariates in sensitivity analyses. GLP-1RA users included patients exposed to a variety of different GLP-1RA agents (47.7% liraglutide, 38.8% exenatide, 12.5% dulaglutide and 1% other). The study demonstrated similar benefit across different members of the GLP-1RA class. Given published preclinical data revealing significant reduction in lung IL-13 downstream of the IL-33/ILC2 pathway in lean and obese mouse models, the authors hypothesized that GLP-1RA use reduced serum periostin. Periostin is in the IL-13 pathway and thus a valuable biomarker, given the difficulty of measuring IL-13. Biobank serum samples were identified from asthmatic individuals with T2D taking a GLP-1RA and propensity score matched to asthmatic individuals with T2D not taking a GLP-1RA. In these cross-sectional samples, GLP-1RA users had a 30% lower serum periostin level [36]. These results suggest GLP-1RA use in adult asthmatic individuals with T2D reduces asthma exacerbation risk independently of improved glycaemic control or weight loss, presumably by downregulation of key airway inflammation pathways.

Recently, a clinical trial ‘Glucagon-like peptide-1 receptor Agonist Treatment in Adult, obesity-related, symptomatic asthma’ (GATA-3) was funded by the National Institutes of Allergy and Infectious Diseases (U01AI155299-01). This prospective trial seeks to address some of the knowledge gaps regarding efficacy of GLP-1RAs on asthma control and tissue-specific effect on allergic airway and adipose inflammation independent of weight loss and change in glycaemic control [37[¶]]. This trial is a double-blind, randomized, placebo-controlled study of semaglutide in adults with obesity-related, symptomatic asthma without T2D, based on the hypotheses that semaglutide improves asthma control, is tolerated, and reduces type 2 and non-type 2 airway inflammation independent of weight loss. Clinical and mechanistic outcomes are planned and inflammatory changes from baseline will be assessed in subcutaneous abdominal adipose and respiratory tract samples. Targeting a metabolic pathway upstream of airway inflammation represents a paradigm shift in the approach to therapeutic intervention in asthma.

CONCLUSION

GLP-1R signalling remains an attractive target for the management of asthma as an anti-inflammatory agent that is glucocorticoid-sparing and may even be disease modifying. The existing data from pre-clinical animal and retrospective human studies demonstrate great potential for GLP-1RA as a novel therapy for asthma, and possibly even broadly for inflammatory pulmonary disease. Unfortunately, prospective data remain limited. Randomized prospective clinical trials of GLP-1RA in well phenotyped asthma are underway. A better understanding of the role of endogenous GLP-1R signalling in the lung and the link between asthma and metabolic syndrome will be important to provide targeted asthma therapy to phenotypically distinct patients.

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Conflicts of interest

K.N. Cahill has served on scientific advisory boards for GlaxoSmithKline, Regeneron, Genentech, Sanofi,

Novartis and AstraZeneca and served as a consultant for Ribon Therapeutics and Verantos outside the submitted work. All other authors do not have any competing affiliations or financial interests to disclose.

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