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Evaluating the GLP-1 receptor in managing asthma

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Abstract

Purpose of review: To discuss the role of GLP-1R signaling in reducing lung inflammation and potential use for GLP-1RA in management of asthma.

Recent findings: While GLP-1RA are currently used for the treatment of 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-1R signaling 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 type 2 diabetes or metabolic syndrome. Retrospective clinical studies demonstrate promising evidence for the use of GLP-1RA in comorbid diabetes and asthma, although prospective human studies are limited.

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

Keywords

airway inflammation; asthma; glucagon-like peptide-1 (GLP-1); interleukin-33 (IL-33); type 2 inflammation

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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 US 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 signaling represents a promising target for modulating airway inflammation. Though 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 multi-systemic anti-inflammatory effects with benefits that extend beyond weight loss and controlling hyperglycemia. Administration of exogenous GLP-1R agonists (GLP-1RA) in animal models is protective in models of pulmonary inflammation [2–5]. Recent retrospective reviews in humans with comorbid T2D and asthma have echoed similar findings [6▪–8]. Thus, targeting the GLP-1R remains enticing for the management of asthma, as GLP-1RA are widely available and already highly effective, multi-purpose drugs for diabetes and obesity – conditions that are often comorbid with asthma.

I. Biology of GLP-1 and current uses

Derived from the post-translational 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 euglycemia by suppressing glucagon secretion and slowing gastric emptying, which reduces food intake, moderates postprandial hyperglycemia, and normalizes fasting hyperglycemia.

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, β2 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 non-specific, thereby making it hard to characterize the true expression of GLP-1R by common techniques.

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

II. Role for GLP-1R signaling beyond glycemic control

GLP-1R is expressed abundantly in numerous organs aside from the pancreas and GI tract, including the heart, lung, brain, and kidney [13]. While GLP-1R signaling in satiety and glycemic control is well-described, the role of GLP-1R signaling 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].

IIa. GLP-1R signaling 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+ 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 to other types of obstructive airway disease, obstruction is reversible, but chronic inflammation can result in airway remodeling (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 remodeling [19].

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

IIb. GLP-1R signaling 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 re-treatment with exendin-4 resulted in over-expression 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-kB in response to OVA challenge, possibly via PKA-dependent mechanism [2]. In another mouse study, a decrease in cAMP within dendritic cells (DC) was associated with increased DC-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-1RA and metformin had relatively higher average forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) compared to those on metformin alone or metformin and insulin [22]. These findings were robust after accounting for change in HbA1c. Weight loss on treatment, which is known to improve lung function in asthma, and was not accounted for in this small cohort study. The exact mechanism of benefit of GLP-1RA 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-1RA 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 signaling in the lung is likely multifactorial and much more 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].

III. GLP-1RA: An attractive agent for comorbid obese asthma?

60% 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 heterogenous 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, also known as “eosinophilic,” asthma is thought to have more of a classic, steroid-responsive, phenotype, while Th2-low, 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 non-obese counterparts [31].

One study using TALLYHO mice, a polygenic mouse model of obesity, demonstrated a promising role of GLP-1RA in these comorbid conditions (Figure 1). Compared to 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 to 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 aforementioned allergen-induced endpoints in TALLYHO 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■]. In another mouse model of obesity, liraglutide reduced LPS-induced ALI by downregulating NLRP3 inflammasome and IL-1β [32]. Similar findings were demonstrated in a lean mouse model of asthma [23]. These studies suggest that GLP-1R signaling may act through a unique, non-steroidal 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 signaling. It is thought that arginine metabolism and nitric oxide (NO) homeostasis is dysregulated in obesity [33]. One possible mechanism of GLP-1R signaling is that GLP-1RA may inhibit asymmetric dimethylarginine, an arginine gene product that is a competitive inhibitor NO synthase [34].

IV. GLP-1RA in human studies

In a pilot observational cohort study, 9 non-smoker patients with asthma – 7 of whom remained on liraglutide, 2 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 7 patients on liraglutide had clinical deterioration in their asthma [35]. While 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; HR 0.52, 95% CI 0.32–0.85). They also had a lower risk of exacerbations – 13/1000 person years fewer. Of note, confidence intervals were wider when stratified for specific diseases, including asthma, as there was a small overall number of events. A meta-analysis which included patients from multiple large clinical trials investigating the potential cardiac benefits of GLP-1RA agonists found a trend towards decreased pulmonary events in those on GLP-1RA compared to 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-1RA compared to other antidiabetic agents [7■■]. Using electronic health record data, asthma exacerbations, defined as a systemic glucocorticoid prescription, were assessed between asthmatics with T2D initiating either a GLP-1RA or other T2D agent. Using a Poisson regression model, patients initiating GLP-1RA experienced substantially fewer asthma exacerbation events within six months of treatment initiation compared with patients initiating long-acting insulins, SGLT-2

inhibitors, sulfonylureas, and DDP-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 the 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 asthmatics with T2D taking a GLP-1RA and propensity score matched to asthmatics 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 asthmatics with T2D reduces asthma exacerbation risk independently of improved glycemic control or weight loss, presumably by downregulation of key airway inflammation pathways.

Recently, a double-blind, randomized, placebo-controlled trial “Glucagon-like peptide-1 receptor Agonist Treatment in Adult, obesity-replated, 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-1RA on asthma control and tissue specific effect on allergic airway and adipose inflammation independent of weight loss and change in glycemic control [37■]. This trial is a double-blind, randomized, placebo-controlled study of semaglutide in adult subjects 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 signaling 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 preclinical 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 signaling 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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Abbreviations used in this paper:

GLP-1	glucagon-like peptide-1
GLP-1R	GLP-1 receptor
T2D	type 2 diabetes mellitus
GLP-1RA	GLP-1R agonists
GPCR	G-protein coupled receptor
cAMP	cyclic adenosine monophosphate
PKA	protein kinase A
FDA	Food and Drug Administration
LPS	lipopolysaccharide
ALI	acute lung injury
OVA	ovalbumin
Th2	CD4+ T-helper type 2
ILC2s	group 2 innate lymphoid cells
IL-33	interleukin-33
DC	dendritic cells
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
Th2-high	type 2 inflammation high
Th2-low	type 2 inflammation low
BALF	bronchoalveolar lavage fluid
TSLP	thymic stromal lymphopoietin
NO	nitric oxide
DPP-IV	dipeptidyl peptidase IV

GATA-3	"Glucagon-like peptide-1 receptor Agonist Treatment in Adult, obesity-replated, symptomatic asthma"

References

Papers of interest have been highlighted as:

■ of special interest

■■ of outstanding interest

[1]. Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000–2016. Geneva, World Health Organization. 2018.

[2]. Zhu T, Wu X-L, Zhang W, et al. Glucagon Like Peptide-1 (GLP-1) Modulates OVA-Induced Airway Inflammation and Mucus Secretion Involving a Protein Kinase A (PKA)-Dependent Nuclear Factor-κB (NF-κB) Signaling Pathway in Mice. Int J Mol Sci. 2015;16:20195–20211. [PubMed: 26343632]

[3]. Sato T, Shimizu T, Fujita H, et al. GLP-1 Receptor Signaling Differentially Modifies the Outcomes of Sterile vs Viral Pulmonary Inflammation in Male Mice. Endocrinology. 2020;161.

[4■]. Toki S, Newcomb DC, Printz RL, et al. Glucagon-like peptide-1 receptor agonist inhibits aeroallergen-induced activation of ILC2 and neutrophilic airway inflammation in obese mice. Allergy. 2021;In a polygenic mouse model of obesity, liraglutide decreased ICAM-1 expression on lung epithelial cells, lung tissue IL-5, IL-13, CCL11, CXCL1, and CXCL5, BALF IL-33, and lung neutrophilia.

[5]. Bloodworth MH, Rusznak M, Pfister CC, et al. Glucagon-like peptide 1 receptor signaling attenuates respiratory syncytial virus-induced type 2 responses and immunopathology. J Allergy Clin Immunol. 2018;142:683–687.e12. [PubMed: 29678751]

[6■]. Albogami Y, Cusi K, Daniels MJ, et al. Glucagon-Like Peptide 1 Receptor Agonists and Chronic Lower Respiratory Disease Exacerbations Among Patients With Type 2 Diabetes. Diabetes Care. 2021;Patients with comorbid T2D and chronic lower respiratory disease on GLP-1RA had lower risk of hospitalization for exacerbation of pulmonary disease compared to those on DPP-IV inhibitors.

[7■■]. Foer D, Beeler PE, Cui J, et al. Asthma Exacerbations in Patients with Type 2 Diabetes and Asthma on Glucagon-like Peptide-1 Receptor Agonists. Am J Respir Crit Care Med. 2021;203:831–840. [PubMed: 33052715] First large retrospective review to demonstrate that use of GLP-1RA in patients with type 2 diabetes and asthma is associated with reduced asthma exacerbations.

[8]. Wei J-P, Yang C-L, Leng W-H, et al. Use of GLP1RAs and occurrence of respiratory disorders: A meta-analysis of large randomized trials of GLP1RAs. Clin Respir J. 2021;

[9]. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology. 2007;132:2131–2157. [PubMed: 17498508]

[10]. Billington CK, Ojo OO, Penn RB, et al. cAMP regulation of airway smooth muscle function. Pulm Pharmacol Ther. 2013;26:112–120. [PubMed: 22634112]

[11]. Rogliani P, Calzetta L, Capuani B, et al. Glucagon-Like Peptide 1 Receptor: A Novel Pharmacological Target for Treating Human Bronchial Hyperresponsiveness. Am J Respir Cell Mol Biol. 2016;55:804–814. [PubMed: 27447052]

[12]. Körner M, Stöckli M, Waser B, et al. GLP-1 receptor expression in human tumors and human normal tissues: potential for in vivo targeting. J Nucl Med Off Publ Soc Nucl Med. 2007;48:736–743.

[13]. Pyke C, Heller RS, Kirk RK, et al. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. Endocrinology. 2014;155:1280–1290. [PubMed: 24467746]

[14]. Viby N-E, Isidor MS, Buggeskov KB, et al. Glucagon-like peptide-1 (GLP-1) reduces mortality and improves lung function in a model of experimental obstructive lung disease in female mice. Endocrinology. 2013;154:4503–4511. [PubMed: 24092637]

[15]. Zhu T, Li C, Zhang X, et al. GLP-1 Analogue Liraglutide Enhances SP-A Expression in LPS-Induced Acute Lung Injury through the TTF-1 Signaling Pathway. Mediators Inflamm. 2018;2018:3601454. [PubMed: 29950925]

[16]. Gou S, Zhu T, Wang W, et al. Glucagon like peptide-1 attenuates bleomycin-induced pulmonary fibrosis, involving the inactivation of NF-κB in mice. Int Immunopharmacol. 2014;22:498–504. [PubMed: 25111852]

[17]. Schmitz J, Owyang A, Oldham E, et al. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. Immunity. 2005;23:479–490. [PubMed: 16286016]

[18]. Pecaric-Petkovic T, Didichenko SA, Kaempfer S, et al. Human basophils and eosinophils are the direct target leukocytes of the novel IL-1 family member IL-33. Blood. 2009;113:1526–1534. [PubMed: 18955562]

[19]. Chan BCL, Lam CWK, Tam L-S, et al. IL33: Roles in Allergic Inflammation and Therapeutic Perspectives. Front Immunol. 2019;10:364. [PubMed: 30886621]

[20]. Toki S, Goleniewska K, Reiss S, et al. Glucagon-like peptide 1 signaling inhibits allergen-induced lung IL-33 release and reduces group 2 innate lymphoid cell cytokine production in vivo. J Allergy Clin Immunol. 2018;142:1515–1528.e8. [PubMed: 29331643]

[21]. Lee J, Kim TH, Murray F, et al. Cyclic AMP concentrations in dendritic cells induce and regulate Th2 immunity and allergic asthma. Proc Natl Acad Sci U S A. 2015;112:1529–1534. [PubMed: 25605931]

[22]. Rogliani P, Matera MG, Calzetta L, et al. Long-term observational study on the impact of GLP-1R agonists on lung function in diabetic patients. Respir Med. 2019;154:86–92. [PubMed: 31228775]

[23]. Xu J, Wei G, Wang J, et al. Glucagon-like peptide-1 receptor activation alleviates lipopolysaccharide-induced acute lung injury in mice via maintenance of endothelial barrier function. Lab Investig J Tech Methods Pathol. 2019;99:577–587.

[24]. Zhou F, Zhang Y, Chen J, et al. Liraglutide attenuates lipopolysaccharide-induced acute lung injury in mice. Eur J Pharmacol. 2016;791:735–740. [PubMed: 27756605]

[25]. Suzuki T, Tada Y, Gladson S, et al. Vildagliptin ameliorates pulmonary fibrosis in lipopolysaccharide-induced lung injury by inhibiting endothelial-to-mesenchymal transition. Respir Res. 2017;18:177. [PubMed: 29037205]

[26]. Nohara H, Nakashima R, Kamei S, et al. Intratracheal GLP-1 receptor agonist treatment up-regulates mucin via p38 and exacerbates emphysematous phenotype in mucus hypersecretory obstructive lung diseases. Biochem Biophys Res Commun. 2020;524:332–339. [PubMed: 31996306]

[27]. Vara E, Arias-Díaz J, Garcia C, et al. Glucagon-like peptide-1(7–36) amide stimulates surfactant secretion in human type II pneumocytes. Am J Respir Crit Care Med. 2001;163:840–846. [PubMed: 11282754]

[28]. Schatz M, Hsu J-WY, Zeiger RS, et al. Phenotypes determined by cluster analysis in severe or difficult-to-treat asthma. J Allergy Clin Immunol. 2014;133:1549–1556. [PubMed: 24315502]

[29]. Telenga ED, Tideman SW, Kerstjens H a., et al. Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response. Allergy. 2012;67:1060–1068. [PubMed: 22686834]

[30]. Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med. 2008;178:218–224. [PubMed: 18480428]

[31]. McCravy M, Ingram JL, Que LG. Dysregulated Metabolism in the Pathophysiology of Non-Allergic Obese Asthma. J Asthma Allergy. 2021;14:179–186. [PubMed: 33692628]

[32]. Hur J, Kang JY, Kim YK, et al. Glucagon-like peptide 1 receptor (GLP-1R) agonist relieved asthmatic airway inflammation via suppression of NLRP3 inflammasome activation in obese asthma mice model. Pulm Pharmacol Ther. 2021;67:102003. [PubMed: 33588055]

[33]. Singh VP, Aggarwal R, Singh S, et al. Metabolic Syndrome Is Associated with Increased Oxo-Nitrative Stress and Asthma-Like Changes in Lungs. PloS One. 2015;10:e0129850. [PubMed: 26098111]

[34]. Ojima A, Ishibashi Y, Matsui T, et al. Glucagon-like peptide-1 receptor agonist inhibits asymmetric dimethylarginine generation in the kidney of streptozotocin-induced diabetic rats by blocking advanced glycation end product-induced protein arginine methyltranferase-1 expression. Am J Pathol. 2013;182:132–141. [PubMed: 23159951]

[35]. Khan F, Mat A, Hogan AE, et al. Preliminary asthma-related outcomes following glucagon-like peptide 1 agonist therapy. QJM Mon J Assoc Physicians. 2017;110:853–854.

[36]. Foer D, Beeler P, Cui J, et al. Glucagon-like peptide-1 receptor agonists decrease systemic Th2 inflammation in asthmatics. J Allergy Clin Immunol. 2020;145:AB241.

[37■]. Cahill KN, Bernard GR. Glucagon-Like Peptide-1 Receptor Agonist Treatment in Adult, Obesity-Related, Symptomatic Asthma [Internet]. NIH Report. Available from: https://reporter.nih.gov/project-details/10084583.First prospective, double-blind, placebo-controlled clinical trial investigating the GLP-1RA in asthma.

Key Points

- GLP-1RA are currently approved for use in T2D and weight loss; however, preclinical evidence suggests broader anti-inflammatory effects and applications for use.
- GLP-1R signaling 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 signaling remains an attractive target for the management of asthma as an anti-inflammatory agent that is glucocorticoid-sparing and may even be disease modifying.

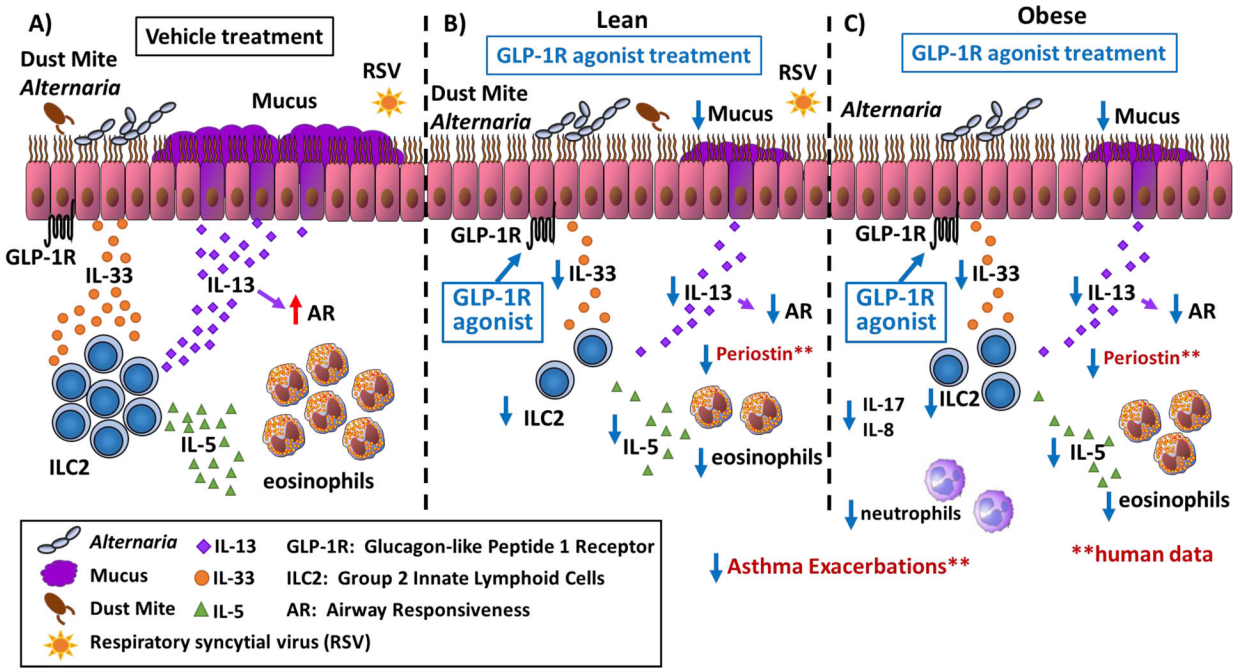

Figure 1.

GLP-1R agonist treatment significantly reduces lung IL-33 release, ILC2 recruitment, eosinophilic and neutrophilic inflammation, T2 and non-T2 cytokine production and airway hyperresponsiveness across multiple challenge model systems and reduces the IL-13 pathway biomarker periostin and asthma exacerbation risk in human studies. **Panel A)** *Alternaria* extract, dust mite, and respiratory syncytial virus challenged mice develop increased airway inflammation. **Panel B)** Pre-treatment with a GLP-1R agonist in lean mice reduced airway inflammation pathways resulting from *Alternaria* extract, dust mite, and RSV challenge. **Panel C)** Treatment with a GLP-1R agonist in obese mice reduces T2 and non-T2 airway inflammation pathways resulting from *Alternaria* extract challenge. **Clinical data supports the IL-13 pathway biomarker periostin and asthma exacerbation risk are reduced in adults with type II diabetes mellitus and asthma exposed to GLP-1R agonists.

Table 1.

Currently available GLP-1R agonists

GLP-1 Receptor Agonists
Dulaglutide
Exenatide
Liraglutide†
Lixisenatide
Semaglutide†‡

† FDA-approved for indication of chronic weight management in obesity

‡ only GLP-1RA currently also available in oral form; all others are subcutaneous injections