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REVIEW

The effects of cigarette smoke on airway inflammation in asthma and COPD: Therapeutic implications

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Summary
Asthma and COPD are two chronic inflammatory disorders of the airway characterized by airflow limitation. While many similarities exist between these two diseases, they are pathologically distinct due to the involvement of different inflammatory cells; predominantly neutrophils, CD8 lymphocytes in COPD and eosinophils and CD4 lymphocytes in asthma. Cigarette smoking is associated with accelerated decline of lung function, increased mortality, and worsening of symptoms in both asthma and COPD. Furthermore, exposure to cigarette smoke can alter the inflammatory mechanisms in asthma to become similar to that seen in COPD with increasing CD8 cells and neutrophils and may therefore alter the response to therapy. Cigarette smoke exposure has been associated with a poor response to inhaled corticosteroids which are recommended as first line anti-inflammatory medications in asthma and as an add-on therapy in patients with severe COPD with history of exacerbations. While the main proposed mechanism for this altered response is the reduction of the histone deacetylase 2 (HDAC2) enzyme system, other possible mechanisms include the overexpression of GR-β, activation of p38 MAPK pathway and increased production of inflammatory cytokines such as IL-2, 4, 8, TNF-α and NF-Kß. Few clinical trials suggest that leukotriene modifiers may be an alternative to corticosteroids in smokers with asthma but there are currently no drugs which effectively reduce the progression of inflammation in smokers with COPD. However, several HDAC2 enhancers including low dose theophylline and other potential anti-inflammatory therapies including PDE4 inhibitors and p38 MAPK inhibitors are being evaluated.

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Introduction

Tobacco was first introduced in the UK during the sixteenth century by Sir Walter Raleigh and was promptly recommended to treat many medical complaints, one being respiratory diseases.[1] In the seventeenth century, smoking the leaves of the Datura plant that contain anticholinergic compounds was a common practice recommendation to treat airway diseases, and such "cures" were used until adrenaline was first introduced for clinical use in the early twentieth century. However, a few decades later, increasing recognition of the harmful effects of tobacco smoke on asthmatics in terms of both the development and aggravation of the condition became apparent.[2,3]

Current estimates show that the prevalence of active cigarette smoking in Europe is 29%, whereas the rate is lower in the US at 21%.[4,5] Accurate data are not available for the proportion of patients with asthma who smoke, however, available information suggest that the rates may be similar to that of the general population.[6] In the NHANES III database, airflow obstruction was present in 14.2% of white male and 13.6% white females who were current smokers.[7]

Both asthma and COPD are chronic inflammatory disorders of the airways whose symptoms arise from airflow obstruction. In both diseases, there is a gene—environmental interaction. In asthma, exposures to environmental allergen are the main triggers for this disease while cigarette smoking is the predominant cause of COPD. Exposure to environmental tobacco smoke (second-hand smoke) has been linked to asthma in early childhood exposure and active smoking has been associated with a rapid decline in lung function in asthma and COPD.[8] Smoking cessation is therefore recommended as the primary goal of the management in these patients. In COPD, smoking cessation has shown to slow the decline in lung function and to prolong survival.[9,10]

While both asthma and COPD are characterized by chronic airway inflammation, key inflammatory cells involved in COPD (macrophages, neutrophils, CD8+ lymphocytes) are different from those involved in asthma (CD4+ Th2 lymphocytes, eosinophils) suggesting different treatments may be required.[11] Although asthma and COPD represent two distinct diseases, these two conditions can occasionally coexist. This may be particularly seen in patients with asthma who have been exposed to cigarette smoke, who can develop fixed airflow limitation and a mixture of "asthma-like" and "COPD-like" inflammation.[6] Furthermore, patients with COPD may have a mixed inflammatory pattern with increased eosinophils similar to that seen in asthma[12] especially during exacerbations. It is therefore not surprising that treatments for both these diseases may often overlap.

In addition to its effect on the course of the two diseases, cigarette smoke greatly reduces the efficacy of some of the important treatment regimens currently available for both conditions particularly inhaled corticosteroids.[13—15] The purpose of this review is to highlight potential mechanisms of how smoking affects the response to the usual treatment regimens for these diseases, and review potential alternative pharmacological therapies which are currently available or under development.

Effects of cigarette smoke on asthma and COPD

Lung function/disease course

Cigarette smoking is associated with accelerated decline of lung function in asthmatics[16,17] worsening asthma severity,[18,19] reduction of responsiveness to glucocorticoids[13,14] and poor asthma control and higher hospital admissions.[20,21] Smokers with asthma also have a greater

need for rescue medications[22] and increased morbidity and mortality rates compared to non-smokers with asthma[18] [Table 1]. In COPD, active cigarette smoking is the most encountered risk factor and is associated with accelerated decline in FEV_1[10] and a higher mortality rate[23] when compared to patients with COPD who are non-smokers.[24–26] [Table 2].

Airway inflammation

The exact mechanisms responsible for the adverse effects seen in asthmatics and COPD who are active smokers are uncertain but believed to be due to increased airway inflammation and reduced corticosteroid responsiveness.[27] Increased T-lymphocytes, mainly CD8 cells[28] and macrophages within the airway wall and infiltration of peripheral airways with mononuclear cells and macrophages[29] have been noted in normal smokers. Heightened sputum neutrophil counts within bronchial secretions are also seen in normal smokers and when this is elevated, increased sputum concentrations of IL-8 are also observed.[13] There is also a positive correlation between neutrophil counts and IL-8 levels with smoking history in pack years and negative correlation with predicted FEV_1. Reduced sputum eosinophil counts have been described in normal smokers compared to non-smokers.[30] Possible mechanisms for the reduced eosinophil count could be the increased apoptosis of activated eosinophils due to exposure the nitric oxide found in cigarette smoke or the carbon monoxide, also present, which may interact with heme proteins.[31,32]

The change in inflammatory mediators that occur in smokers reinforces the idea that smokers with asthma develop pathological features similar to COPD. Sputum abnormalities, however, are not homogenous across all patients as some groups of smokers with asthma have similar findings to non-smokers.[33] This suggests that differences in intensity of smoking and duration of smoking and phenotype of asthma may influence the inflammatory profile seen in the airway of smokers with asthma.

A recent study reported reduced number of CD83 + ve mature dendritic cells and B lymphocytes in asthmatic smokers compared to those with the condition who never smoked.[34] These results were derived from one of the first bronchial biopsy studies of the large airway of smokers and non-smokers. The authors speculated that these results may explain the higher number of lower respiratory tract infections present in smokers with asthma. In animals, smoking altered the IgE response and increased the sensitization to allergens.[35] Indeed, a recent study showed total IgE levels were higher in smokers compared to non-smokers with asthma.[36] The authors suggested that smoking might play a role in IgE secretion from B cells; however, the exact mechanism is still unknown. The study demonstrated that 37.5% of asthmatic patients who were active or former smokers showed decrease pulmonary function and increased IgE, emphysema on high resolution computed tomography and fixed airway obstruction. However, the role on anti-IgE therapy in this population has not been evaluated.

Table 1 Effects of cigarette Smoke on clinical outcomes in asthma.

	Smokers	Non-Smokers
FEV_1 Decline (% change from FEV_1 predicted age 18 and 40)[a]	−17.8	−10.1
Hospitalization Rates (%)[b]	58	42
Mortality Rates (OR)[c]	3.6	1

[a] A study of 4000 adults initially aged 18–30 yrs, who were followed for over 10 yrs with serial spirometry measurements. This was a subgroup within the study comparing asthmatics who didn't smoke with asthmatics who smoked at least 15 cigarettes/day.[16]

[b] A study of 1847 patients between 18 and 54 yrs, who presented to the emergency department with acute asthma. Current and former smokers together made up 58% of admissions.[21]

[c] A study of 6 year mortality rate following a near-fatal asthma attack with an age-adjusted odds ratio (OR).[18]

Table 2 Effects of cigarette Smoke on clinical outcomes in COPD.

	Smokers	Non-Smokers
FEV_1 Decline (mL/5 years)[a]	267	72
Mortality Risk Ratio[b]	2.2–24.7	1

[a] Figures are the cumulative 5 year average decline in FEV_1 for control group (smokers with COPD) and for those with sustained cessation for 5 years (non-smokers with COPD).[10]

[b] Mortality risk ratios for cigarette smokers compared with non-smokers vary markedly, as reported from 8 major prospective studies.[23]

Clinical implications of cigarette smoke exposure in asthma and COPD

The various changes in the inflammatory phenotype observed in smokers with asthma and COPD have suggested several potential mechanisms that new or existing treatments can target. Data from several clinical trials (carried out in asthmatics who were never smokers or former smokers) have led to guidelines emphasizing the need for inhaled corticosteroids as first line therapy in patients with chronic asthma as the most effective anti-inflammatory therapy for this condition.[37,38] Studies have shown that inhaled corticosteroids lead to a reduction in asthma symptoms, improvement in lung function and quality of life, and a reduction in airway inflammation and airway hyper-responsiveness. Furthermore, studies have shown that these drugs reduce the frequency and severity of exacerbations and reduce asthma mortality.

However, these beneficial effects are reduced in asthmatics who are active smokers as shown in several studies.[13,14,39,40] In one study, short-term inhaled corticosteroid treatment in active cigarette smokers failed to cause significant changes in mean morning peak expiratory flow (PEF), mean FEV_1 and geometric mean PC20 to methacholine when taking 1000ug of fluticasone propionate daily for 3 weeks.[13] Non-smokers who participated in this randomized placebo-controlled trial showed significant increases in these parameters as well as a decrease in

sputum eosinophils compared to placebo; findings not seen in active cigarette smokers.

Furthermore, active smoking impairs the efficacy of short-term oral corticosteroid treatment in chronic asthma.[14] A randomized, placebo-controlled, crossover study assessed smokers with asthma, ex-smokers with asthma, and never smokers with asthma who took prednisolone (40 mg daily) or placebo for 2 weeks (all patients had $\geq$15% reversibility of FEV_1 after nebulized salbutamol and a mean post-bronchodilator % predicted of more than 80%). Never smokers showed significant improvement in FEV_1 (237 ml), morning peak expiratory flow (PEF) (36.8 L/min) and asthma control score ($-$0.72). There were no significant changes in any of the scores for smokers and in subjects that were ex-smokers, treatment with prednisolone led to an improvement in morning and night PEF only (29.1 and 52.36 L/min respectively).

There continues to be major controversies with regards to treating COPD patients with inhaled corticosteroids. While some studies demonstrated a significant effect of inhaled corticosteroids in reducing the overall exacerbation rate in patients with moderate-to-severe COPD (FEV_1 <50% predicted)[41] and improving health status,[42] arguments against their as regular treatment are numerous and arise from studies showing that their use does not reduce the long term decline of FEV_1 seen in these patients with COPD,[41,43,44] does not reduce overall mortality and increases the probability of adverse effects including pneumonia.[45,46] As a result of the lack of evidence for their benefits, and increasing evidence of potential detrimental side effects, inhaled corticosteroids are not recommended as first line therapy for patients with COPD, but are used as add-on therapies in patients with severe and very severe COPD to reduce exacerbations.

Taking into account all of these studies, the results suggest cigarette smoke exposure in patients with asthma or COPD is associated with relative resistance to corticosteroid therapy. Understanding the mechanism of this resistance may help the development of treatment which can restore corticosteroid sensitivity/which may improve clinical outcomes.

Mechanisms of corticosteroid resistance induced by cigarette smoke

Studies showing reduced effects of corticosteroids in smokers with asthma and COPD have led to the implication of various mechanisms involved in this resistance (Table 3).

HDAC2 dysfunction

Perhaps the most important mechanism that may explain the relative corticosteroid resistance in smokers with asthma and COPD is reduction in the enzyme histone deacetylase 2 (HDAC2). Inflammatory genes activated in both conditions lead to the acetylation of core histones. This acetylation causes the opening up of the chromatin structure, subsequent gene transcription and synthesis of inflammatory proteins (Fig. 1).[47,48] For corticosteroids to exert their maximal effects in terms of pro-inflammatory cytokine suppression, HDAC2 activity is required. It has been previously shown that glucocorticoids act through the glucocorticoid receptor (GR) by recruiting HDAC2 to the activating transcription factor complex, preventing acetylation.[47] Smoking reduces the activity of HDAC2 in inflammatory cells such as alveolar macrophages, which may explain the increased expression of inflammatory mediators seen in lavage samples of smokers.[49] The decrease in HDAC2 activity with smoking is possibly a result of oxidative stress, which impairs its function as shown *in vitro* in primary airway epithelial cells from healthy volunteers.[49] The nature of this oxidative stress is not known, however, high levels of nitric oxide present in tobacco smoke are thought to generate peroxynitrite.[50] Peroxynitrite nitrates tyrosine residues on HDAC2 and nitrotyrosine formation in the alveolar macrophages of COPD patients has been documented.[51] Drugs that increase the level of HDAC2 in smokers show real promise as they have the potential to restore corticosteroid sensitivity as will be discussed.

Glucocorticoid receptor β\

An increase in the number of neutrophils found in the airway in heavy smokers who have asthma has also been associated with poor corticosteroid response.[52] It is believed that overexpression of the glucocorticoid receptor β isoform (GR-β) inhibits the action of the ligand-activated glucocorticoid receptor alpha (GR-α), the functional isoform, through which the effects of glucocorticoids are mediated.[53–55] Since neutrophils have a higher number of GR-β, this may explain the poor corticosteroid response seen in smokers.

Table 3 Potential therapeutic options in smokers with asthma and COPD.

Drugs class	Examples
Smoking Cessation	Nicotine Replacement Therapy Buproprion Varenicline
ICS, ICS/LABA combination	Fluticasone/Salmeterol Budesonide/Formoterol Mometasone/Formoterol
Long-acting Anticholinergics	Tiotropium
Leukotriene Modifiers	Montelukast Zileuton
HDAC2 Enhancers	Theophylline Peroxynitrite Scavenger Drugs Macrolides
Peroxisome Proliferator-Activated Receptor Agonists	Rosiglitazone
Other Anti-Inflammatory Agents	PDE4 Inhibitors P38 MAPK inhibitor TNF $-$ α inhibitors

ICS = Inhaled corticosteroids, LABA = Long-acting beta2-agonists, HDAC2 = Histone deacetylase 2.

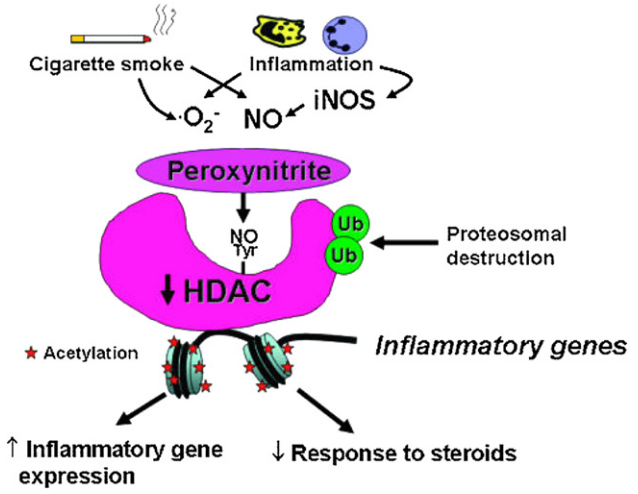

Figure 1 [48] Possible mechanisms for decreased HDAC-2 activity in smokers with asthma and COPD. Cigarette smoke produces superoxide anions and nitric oxide which with inflammatory cells such as neutrophils produce peroxynitrite. Peroxynitrite may lead to inactivation of HDAC-2 via nitration and ubiquitination. Inactivation of HDAC-2 results in increased inflammatory gene expression and reduced response to anti-inflammatory actions of corticosteroids. Adapted from[48] with permission.

Altered inflammatory cytokines

In patients with corticosteroid-resistant asthma, airway T cells were reported to have increased levels of IL-2 and IL-4 gene expression when compared to asthmatics who were responsive to corticosteroids.[56] The cytokines, IL-2 and IL-4 when combined *in vitro*, lead to reduced corticosteroid response by causing a defect in peripheral blood mononuclear cell glucocorticoid receptor binding affinity.[57] This is thought to be due to an increase in GR-β caused by higher levels of IL2 and IL4.[54] Similarly it has been shown that smoking leads to an increase in the production of pro-inflammatory cytokines IL4, IL-8 and TNF-α, both *in vitro* and *in vivo*.[13,58,59] While the precise mechanisms of how these cytokines impair corticosteroid response are unknown, it has been suggested to be due to raised GR-β expression.[60,61] Nuclear factor-Kβ (NF-Kβ) has also been linked to corticosteroid unresponsiveness in Crohn's disease[62] and is thought to play a similar role in smokers. This is because bacterial lipopolysaccharide (LPS) present in cigarette smoke is an activator of NF-Kβ,[63] and this activated form is associated with the induction of pro-inflammatory cytokines TNF-α and IL-8. Furthermore NF-Kβ can lead to phosphorylation of the GR, inhibiting GR-α function and therefore, its ability to bind onto DNA and lead to desired effect.[64]

The p38 mitogen-activated protein kinase (MAPK) pathway is also thought to play a role in corticosteroid insensitivity. This is because LPS stimulates bronchoalveolar cells that lead to the activation of p38 MAPK at a more rapid pace in smokers than in non-smokers.[50] This leads to phosphorylation of GR, which results in reduced affinity between the corticosteroid and the receptor.[65]

In summary, several mechanisms have been put forward to explain the corticosteroid insensitivity identified in asthmatic smokers and COPD patients. It is possible that not a single one is responsible but several of them may be acting together.

Current and future targets for therapy

Smoking cessation

Even though it is unclear whether or not smoking cessation leads to improved corticosteroid responsiveness, the importance of smoking cessation should be reinforced in both these diseases. Studies show that smoking cessation is associated with improved asthma control[66,67] and reduced COPD exacerbations. In one particular study, patients with asthma who stopped smoking showed significant improvement in lung function in the short term and a decrease in neutrophil count when compared to asthma patients who continued to smoke.[68] Smoking cessation in COPD patients can reduce progression[8] and decrease the risk of all-cause mortality, as shown after a 14.5 year follow up study by Anthonisen et al.[10] Although the benefits or stopping are well known, it seems more useful to follow pharmacological management guidelines from an early stage as cessation rates are very low.[69,70]

Pharmacological therapies should supplement the behavioural interventions in approaching patients who want to quit smoking. First-line treatment as recommended by guidelines should include a nicotine replacement therapy, sustained release bupropion or varenicline unless contraindications are present.[71] Varenicline, a partial agonist of selective neuronal nicotinic receptors is approved for use as an aid to smoking cessation treatment and shows significant effects in smokers with mild to moderate COPD.[72]

Increasing dose of inhaled corticosteroids or addition of a long acting bronchodilator

In smokers with asthma who are unable to stop smoking, medication may be required in addition to inhaled corticosteroids or even as a replacement. Increasing the dose of inhaled corticosteroids has been suggested.[73] Tomlinson et al showed that differences in morning PEF and the number of asthma exacerbations between smokers and non-smokers were reduced when patients were given 2000ug inhaled beclomethasone daily instead of 400ug. It should be noted that this study had a small sample size and showed a negative interaction test for a different effect of smoking in the low versus high-dose inhaled corticosteroid group. High doses of ICS have a minimal effect in patients with COPD as they do not affect the rate of decline of lung function nor do they decrease mortality.[74] The only benefit would be a reduction in frequency of exacerbations.

When combined with long-acting β2 agonists (LABA), an inhaled corticosteroid is very effective in the treatment of asthma and COPD, to a greater extent in the former. In asthma, a post-hoc analysis of the Gaining Optimal Asthma ControL (GOAL) study showed combination therapy with fluticasone and salmeterol reduced exacerbation rates

compared to fluticasone alone.[75] With regards to COPD, subjects showed improved pre-treatment FEV_1 significantly more than placebo or either treatment alone, as well as producing clinically significant improvement in health status and a decrease in daily symptoms.[76] In summary, the scientific rationale for this combination takes into account the different aspects of the pathophysiology of asthma/COPD that they both affect.[77] ICSs are known to suppress chronic inflammation and reduce airway responsiveness, while LABAs have bronchodilator actions, inhibit mast cell mediator release and plasma exudation release.[78] In addition, they may also reduce sensory nerve activation. Hence the two drugs have complementary actions that would otherwise be unachieved with either drug alone.

The effects of adding the long-acting anticholinergic agent, tiotropium, to inhaled corticosteroids in non-smokers with asthma adults whose disease was not adequately controlled with a low dose of inhaled corticosteroids were examined in a trial which was just recently published.[79] The study was a triple blind, placebo controlled, three-way crossover trial that aimed to compare three treatments: doubling the dose of inhaled glucocorticoid, adding a twice daily dose of LABA to beclomethasone and adding a once daily dose of tiotropium to beclomethasone. The addition of tiotropium resulted in a larger improvement in both PEF (the primary outcome) and FEV_1 (secondary outcome) when compared to patients who received double the dose of inhaled corticosteroid. What was found to be more surprising was the addition of tiotropium therapy was not inferior to the glucocorticoid and LABA combination. These results may lead some clinicians to replace LABAs with tiotropium in patients who fail to respond to low doses of glucocorticoids, such as those seen in smokers with asthma. However, for more a definitive answer, more studies are required to evaluate the effects of tiotropium in smokers with asthma.

Leukotriene modifiers

Leukotrienes are molecules believed to contribute to airway obstruction seen in asthma. They are produced by mast cells, alveolar macrophages and eosinophils and are derived from the action of 5-lipoxygenase on arachidonic acid.[80–82] It is known that leukotrienes are able to mediate bronchoconstriction,[83] mucus secretion,[84] the recruitment of inflammatory cells[85] and permeability of the microvasculature[86] – all of these considered to be key components of the physiology of asthma. Previous studies have shown that leukotriene synthesis inhibitors or receptor antagonists block the bronchospastic response seen in asthma patients when exposed to allergens, exercise, cold dry air or aspirin.[87–90]

Lazarus and colleagues demonstrated that in mild asthmatics who smoked and who showed corticosteroid insensitivity, montelukast produced a statistically significant increase in morning PEF and a decrease in PEF variability in smokers.[33] Montelukast showed greater effects in smokers than non-smokers. The rationale for this is that previous studies have shown a dose-related increase in urinary leukotriene E4 (LTE4) excretion in regular smokers.[91] Furthermore, an increase in 5-lipoxygenase activity in the airways of smoker without asthma has been noted, as well as an increase in urinary LTE4 caused by smoking in patients with asthma which is not seen in healthy smokers or those with COPD.[92] The results seen from the study by Lazarus and colleagues[33] should be treated with caution as participants only had very mild asthma and the improvement in morning peak flow of montelukast in smokers with asthma was small. These results need to be followed up by a larger prospective study in order for leukotriene receptor antagonists to be recommended as first-line treatment of smokers with asthma.

The role of leukotriene modifiers in COPD is limited based on current clinical trials. However, a recent meta-analysis looking at four placebo-controlled trials of COPD patients treated with leukotriene antagonists, zafirlukast and montelukast, came to the conclusion that these patients showed a significant improvement in FEV_1 and FVC.[93] The role of 5-lipooxygenase inhibitors such as zileuton may be beneficial in smokers with asthma and in COPD. Zileuton has additional effects in comparison to leukotriene receptor antagonists, blocking the formation of cysteinyl leukotrienes, hydroxyeicosatetraenoic acid and leukotriene B4. A study by Israel et al showed patients with asthma taking zileuton for three months experienced fewer asthma exacerbations that required treatment with corticosteroids compared to placebo. Furthermore patients taking zileuton saw an improvement in FEV_1 by 15.7% compared to an improvement of 7.7% seen in the control group.[94] A similar study carried out during the same time period showed patients taking 600 mg and 400 mg of zileuton experiencing greater improvements in FEV, reduced blood eosinophil levels, improved morning PEF rate and reduction in daytime and nocturnal symptoms compared to the placebo group.[95] In a recent study, sixty patients with COPD were given oral zileuton in addition to the usual treatment for exacerbation of COPD requiring hospitilization. Despite being safe and reducing urinary LTE4 levels, there was no difference in hospital length stay or treatment failure compared to placebo. These results may reflect the small nature of the study and larger trials may be required to detect clinical improvement.[96]

HDAC2 enhancers

Drugs which enhance HDAC2 provide real optimism for reversing the corticosteroid insensitivity seen in COPD and asthmatics who smoke. Low–dose theophylline can restore the activity and increase expression of HDAC2 to normal in alveolar macrophages in COPD patients, without side effects that are experienced under high doses.[97] These effects are reversed with an HDAC2 inhibitor, confirming theophylline does activate HDAC2 and does not restore corticosteroid sensitivity via another mechanism. In a murine model of short-term cigarette exposure to induce inflammation similar to that seen in corticosteroid-resistant COPD/asthma, low doses of theophylline effectively reduced lung inflammation only when used in combination with a corticosteroid.[98] It is currently unknown how theophylline activates HDAC2 but it is thought the activation occurs within the nucleus and via inhibition of PI3K as LY-294002; a PI3K inhibitor mimics its action.[99]

Another mechanism for the reduced activity of HDAC2 is by oxidative/nitrative stress. Antioxidants available such as vitamin C and E are not potent enough to reduce oxidative stress in the lung sufficiently.[99] Currently more potent antioxidants and peroxynitrite scavenger drugs are being developed.[100] Curry powder contains a polyphenol, curcumin, which has been found to reverse corticosteroid sensitivity by increasing HDAC2 expression levels to those found in normal individuals in human monocytes exposed to oxidative stress and cigarette smoke.[101]

Macrolides play a role in inhibiting NF-Kβ and it has been shown that a non-antibiotic macrolide increases HDAC2 activity which results in the reversal of corticosteroid resistance, suggesting HDAC2 inhibits NF-Kβ driven inflammation.[102] A recent study, in COPD patients, suggest that the chronic administration (one year) of azithromycin is associated with significant reduction in COPD exacerbation.[103]However, the chronic use of these agents in smokers with asthma needs further studies.

Peroxisome proliferator-activated receptor agonists

Peroxisome proliferator-activated receptors (PPARs) are a family of ligand-activated transcription factors that belong to the nuclear hormone receptor family, of which 3 subtypes are known — PPAR-α, -γ and - δ. PPARs have been shown to be related to glucocorticoid, retinoid and thyroid hormone receptors.[104] Experiments *in vivo* animal models have shown that all 3 of the receptors when activated, lead to anti-inflammatory and immunomodulatory effects in the lung and other tissues, providing a potential novel target for inflammatory diseases.[105] The PPAR-γ agonist rosiglitazone, a member of the thiazolidinediones class, was generating the most interest as this drug was already being used to treat diabetes. Although the main benefits of this drug for diabetes were due to its insulin sensitizing effects, additional benefits were thought to be due to anti-inflammatory properties. Recent research has demonstrated that rosiglitazone is able to bind to the glucocorticoid receptor ligand-binding domain and thereby alter gene transcription.[106] This may result in increased glucocorticoid receptor activation which is otherwise lowered in smokers as previously mentioned. A trial evaluating the effects of rosiglitazone on the lung function of smokers with asthma has recently reported its results.[107] Rosiglitazone produced improvements in prebronchodilator FEV_1 relative to low dose inhaled corticosteroids after 2 (164 ml, $p = 0.051$) and 4 weeks of treatment (183 ml, $p = 0.051$]. This improvement was more substantial than previous studies that assessed the effect of inhaled corticosteroids in asthmatic smokers. Rosiglitazone also showed significant improvements in both forced expiratory flow between 25 and 75% of the forced vital capacity, suggesting a potential use in the treatment of small-airway obstruction, of which few therapies currently exist. The conclusion of this trial was that the PPAR-γ agonist showed improvements in lung function measurements in smokers with mild to moderate asthma. Limitations of the trial include the small number of subjects and short duration of treatment. Further studies are required to see how useful such PPAR-γ agonists could be in treatment-resistant groups such as smokers with COPD and asthma.

Other anti-inflammatory targets

Several selective phosphodiesterase- 4 inhibitors are currently under development which may have an effect on the neutrophilic inflammation seen in COPD. One such agents is roflumilast.[108] While roflumilast is now approved for the treatment of COPD patients with severe disease and with history of COPD exacerbations, it is not currently approved for the treatment of asthma. However, there may be a place for roflumilast in the treatment of smokers with asthma, as when administered over 4 weeks, this drug reduced the number of neutrophils by 36%.[109] This needs further exploration in future studies.

Inhibitors of the p38 MAP kinase cascade may have a role in treating smokers with either condition that are corticosteroid insensitive as this would prevent the reduction of activation of the GR by corticosteroids due to the action of the MAPKs.[65] In COPD patients, p38 MAPK is activated in alveolar macrophages and regulates the expression of inflammatory cytokines including IL-8 and TNF-α, and thus may also play a role in asthmatic smokers.[110] SD-282, an inhibitor of p38, has been shown to be effective in suppressing inflammation in smoking models of COPD in corticosteroid insensitive mice.[111] Problems encountered include severe adverse effects and toxicity that suggests they have to be inhaled in order to reduce systemic exposure.

TNF-α levels are increased in both COPD and asthma and are believed to cause neutrophilic inflammation in the lungs. Infliximab, a recombinant human-murine chimeric monoclonal antibody of TNF-α, caused a decrease in the number of patients with exacerbations in symptomatic moderate asthma and was well tolerated.[112] These results led the authors to recommend larger trials of therapy against TNF-α, especially in patients with more severe forms of asthma. The benefits of infliximab have failed to pass onto patients with COPD. In a placebo-controlled trial with over 200 COPD patients, Rennard and colleagues reported no differences in symptom score (primary endpoint), lung function, exercise capacity, as well as any of the other secondary endpoints.[113] This was unexpected as the inflammatory pattern involving TNF-α in COPD is similar to that found in rheumatoid arthritis and inflammatory bowel disease, where infliximab has been very successful.[114]

Conclusions

Cigarette smoke adversely affects the course and response to therapy in asthma and COPD. There is currently no optimal drug therapy to effectively treat airway inflammation in smokers with asthma or COPD, however, many potential targets for future therapies exist. Since the inflammatory phenotype seen in smokers with asthma is somewhat similar to that seen in COPD, one type of medication may suppress the progression of inflammation in both conditions. The most promising therapies are HDAC2 enhancers, which aim to reverse corticosteroid insensitivity seen in smokers.

Conflict of interest

Asad Tamimi is medical student. Dzelal Serdarevic is Pfizer employee.

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