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Air pollution and resistance to inhaled glucocorticoids: Evidence, mechanisms and gaps to fill☆

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ABSTRACT

Substantial evidence indicates that cigarette smoke exposure induces resistance to glucocorticoids, the primary maintenance medication in asthma treatment. Modest evidence also suggests that air pollution may reduce the effectiveness of these critical medications. Cigarette smoke, which has clear parallels with air pollution, has been shown to induce glucocorticoid resistance in asthma and it has been speculated that air pollution may have similar effects. However, the literature on an association of air pollution with glucocorticoid resistance is modest to date. In this review, we detail the evidence for, and against, the effects of air pollution on glucocorticoid effectiveness, focusing on results from epidemiology and controlled human exposure studies. Epidemiological studies indicate a correlation between increased air pollution exposure and worse asthma symptoms. But these studies also show a mix of beneficial and harmful effects of glucocorticoids on spirometry and asthma symptoms, perhaps due to confounding influences, or the induction of glucocorticoid resistance. We describe mechanisms that may contribute to reductions in glucocorticoid responsiveness following air pollution exposure, including changes to phosphorylation or oxidation of the glucocorticoid receptor, repression by cytokines, or inflammatory pathways, and epigenetic effects. Possible interactions between air pollution and respiratory infections are also briefly discussed. Finally, we detail a number of therapies that may boost glucocorticoid effectiveness or reverse resistance in the presence of air pollution, and comment on the beneficial effects of engineering controls, such as air filtration and asthma action plans. We also call attention to the benefits of improved clean air policy on asthma. This review highlights numerous gaps in our knowledge of the interactions between air pollution and glucocorticoids to encourage further research in this area with a view to reducing the harm caused to those with airways disease.

Contents

Abbreviations: ACTH, adrenocorticotropin; ANOVA, analysis of variance; AP-1, activator protein-1; BAL, bronchioalveolar lavage; CD, cluster of differentiation; CDKN1C, cyclin-dependent kinase inhibitor 1C; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; CRH, corticotropin-releasing hormone; DALYs, disability-adjusted life years; DE, diesel exhaust; DEP, diesel exhaust particulate; DNA, deoxyribonucleic acid; DUSP1, dual specificity protein phosphatase 1; eNO, exhaled nitric oxide; ERK, extracellular signal–regulated kinase; FEV_1, forced expiratory volume in one second; FKBP5, FK506 binding protein 5; FVC, forced vital capacity; GR, glucocorticoid receptor; GRE, glucocorticoid response element; GST, glutathione S-transferase; H_2O_2, hydrogen peroxide; HAT, histone acetylase; HDAC, histone deacetylase; HDM, house dust mite; HEPA, high efficiency particulate air; HPA, hypothalamic-pituitary-adrenal; HRV, human rhinovirus; ICS, inhaled corticosteroids; IFN, interferon; IKK2, inhibitor of NF-κB kinase subunit beta; IL, interleukin; JNK, c-Jun N-terminal kinase; LABA, long-acting beta2-adrenoceptor agonist; MAPK, mitogen-activated protein kinase; miRNA, microRNA; NAC, N-acetylcysteine; NADPH, nicotinamide adenine dinucleotide phosphate; NCOA, nuclear receptor coactivator; NFE2L2/NRF2, nuclear factor-(erythroid-derived 2)-like 2; NF-κB, nuclear factor-kappa B; NO, nitric oxide; NO_2, nitrogen dioxide; NOS, nitric oxide synthase; NO_x, nitrogen oxides; NQO1, NAD(P)H quinone oxidoreductase 1; O_3, ozone; OVA, ovalbumin; PAH, polycyclic aromatic hydrocarbon; PEF, peak expiratory flow; PM, particulate matter; $PM_{2.5}$, particulate matter smaller than 2.5μm; PM_{10}, particulate matter smaller than 10μm; POMC, proopiomelanocortin; ROS, reactive oxygen species; RSV, respiratory syncytial virus; SABA, short acting $beta_2$-adrenoceptor agonist; SO_2, sulfur dioxide; TNF, tumor necrosis factor; TRAP, traffic-related air pollution; TSC22D3, TSC22 domain family protein 3; WHO, world health organization.

☆ We use the terms glucocorticoid and corticosteroid interchangeably throughout this review while inhaled corticosteroid or the acronym (ICS) are used to when describing inhaled clinical use. We have used standard gene symbols from the human genome organization (HUGO) gene nomenclature committee as detailed at www.genenames.org

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1. Scope

The fields of glucocorticoid, glucocorticoid resistance and air pollution biology are all too vast to survey in detail in this review. Instead, we introduce these areas briefly, before focusing on evidence and gaps in our understanding of the interaction of glucocorticoids and air pollution, primarily in the context of asthma. In surveying the landscape of current data on interactions between air pollution and glucocorticoids, we highlight epidemiology, results from animal studies and emerging findings from controlled exposure studies. This review then details mechanisms through which air pollution may affect glucocorticoid function, before finishing with some potential approaches to mitigating harm in the short and longer term. Our hope is that this review encourages more work to reduce the harm of air pollution in respiratory diseases.

2. Introduction

Synthetic corticosteroids (also known as glucocorticoids) are the most effective anti-inflammatory medication for the treatment of a number of conditions, including eczema, rheumatoid arthritis, inflammatory bowel disease and asthma (Barnes & Adcock, 2009). Inhaled corticosteroids (ICS) have become the primary anti-inflammatory therapy for all but the mildest asthmatics, given the recognition that inflammation is usually present in the airways of even those with modest symptoms (Global Initiative for Asthma, 2017). Most asthmatics have their inflammation and symptoms efficiently controlled by modest doses of ICS that do not induce substantial side effects. Nevertheless, some individuals show no, or limited, responses to glucocorticoid, even after accounting for poor adherence to medication and other confounding factors (Keenan, Salem, Fietz, Gualano, & Stewart, 2012). This phenomenon is known as glucocorticoid insensitivity, hyporesponsiveness, or more commonly resistance. While some individuals have mutations in the glucocorticoid receptor (GR; *NR3C1*) leading to primary resistance, most do not (Charmandari, Kino, & Chrousos, 2013; Chrousos et al., 1982). The clinical effectiveness of inhaled glucocorticoids on symptoms of obstructive disease is often variable in a given individual over time, suggesting that dynamic, i.e. non-genetic, factors modulate responsiveness in such cases. For example, both respiratory infections and cigarette smoke have been shown to temporarily reduce responsiveness to glucocorticoids, decreasing symptom control (Newton, 2014; Reddy & Little, 2013). Likewise, emerging evidence suggests that exposure to environmental factors, including air pollution, may reduce the effectiveness of glucocorticoid therapy, in diseases including asthma (Hansbro et al., 2017; Holgate & Polosa, 2006).

2.1. Asthma

Asthma is a chronic inflammatory respiratory disease characterized by symptoms, including airway hyperresponsiveness, excess mucus production and airway remodelling, that currently affects ~300 million individuals worldwide (Anandan, Nurmatov, van Schayck, & Sheikh, 2010; Global Initiative for Asthma, 2017; Masoli, Fabian, Holt, & Beasley, 2004). Furthermore, projections suggest that global prevalence will rise to 400 million by 2025 (Global Initiative for Asthma, 2017). As a chronic disease that can extend from childhood into old age, asthma presents a significant hardship for patients leading to a yearly loss of 14 million disability-adjusted life years (DALYs) and represents ~2% of the total global burden of disease (Global Initiative for Asthma, 2017; Masoli et al., 2004; Peters, Ferguson, Deniz, & Reisner, 2006). Asthma care continues to be very expensive even in developed countries, with, for example, direct (drugs, hospitals, physicians) and indirect costs (long-term disability, mortality) of over $2.2 billion in 2010 in Canada, with projections suggesting expenditures will reach $4.2 billion by 2030 (The Conference Board of Canada et al., 2012). Since the majority of asthma costs derive from medications and hospital admission (Bahadori et al., 2009; Lane, Molina, & Plusa, 2006), expenditure rises dramatically when reduced symptom control leads to an exacerbation. Symptoms of acute bronchoconstriction in asthma are usually treated with β_2-adrenoceptor agonists, which act through multiple mechanisms to relax airways smooth muscle, without decreasing inflammation (Cazzola, Page, Rogliani, & Matera, 2013). Lung inflammation is generally treated with ICS, which decrease asthma symptoms and exacerbation frequency (Barnes, 2016).

2.2. Mechanisms of glucocorticoid activity and resistance

There are numerous vital steps in the mechanisms of synthetic glucocorticoid activity that may be disrupted in the development of resistance. Synthetic glucocorticoids, including budesonide and fluticasone, used to treat asthma, potently mimic the effects of endogenous corticosteroid hormones, such as cortisol and cortisone. Cortisol is released in a circadian manner with a mid-morning peak and in reaction to stress as part of the "fight or flight" response (Sapolsky, Romero, & Munck, 2000). Pain, infection and psychological stress can cause activation of the hypothalamic-pituitary-adrenal (HPA) axis, causing discharge of corticotropin-releasing hormone (CRH) from the hypothalamus and the subsequent release of adrenocorticotropin (ACTH) from the pituitary gland (Herman et al., 2016). ACTH activates the synthesis and release of cortisol from the adrenal glands into the blood.

Cortisol and synthetic glucocorticoids pass through cell membranes and bind to the GR, though cortisol also binds to the mineralocorticoid receptor with equivalent potency (Chrousos, Pavlaki, & Magiakou, 2011). GR is a modular protein containing N-terminal, deoxyribonucleic acid (DNA) binding, hinge and the ligand binding C-terminal domain (Giguère, Hollenberg, Rosenfeld, & Evans, 1986; van der Laan & Meijer, 2008). The N-terminal domain contains an activator function region that interacts with basal transcription machinery and cofactors, but also numerous sites that can be phosphorylated some of which alter GR conformation and activity (Vandevyver, Dejager, & Libert, 2014). The DNA binding region of GRα encompasses a nuclear localization signal and two zinc fingers, which recognize and bind to consensus glucocorticoid response elements (GREs) present in genomic DNA. The C-terminal ligand binding domain contains a second nuclear localization signal and activator function region (Vandevyver et al., 2014).

Alternative splicing of the GR gene *NR3C1* leads to the production of various GR isoforms, including GRα the primary isoform, GRγ which has a distinct transcriptional profile and the C-terminal truncated isoform GRβ, which has lower expression, does not bind glucocorticoids and may act as a dominant repressor of GRα (Bamberger, Bamberger, de Castro, & Chrousos, 1995; Gagliardo et al., 2000; Vandevyver et al., 2014).

Binding by glucocorticoid induces conformational changes in GRα, causing nuclear localization signals to be unmasked and mediating translocation into the nucleus (Picard & Yamamoto, 1987). Once in the nucleus, glucocorticoid-bound GRα may act in at least three ways: 1) to induce the expression of genes (transactivation), many of which have anti-inflammatory properties, 2) to bind to negative GREs reducing transcription, and 3) to bind to pro-inflammatory transcription factors (transrepression), including nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1), reducing their activity (Hua, Ganti, & Chambon, 2016; Newton, Shah, Altonsy, & Gerber, 2017; Oh et al., 2017; Uhlenhaut et al., 2013; Vandevyver, Dejager, Tuckermann, & Libert, 2013). Transrepression occurs predominantly through binding or tethering of GRα to largely pro-inflammatory transcription factors, reducing the ability of the transcription factor to bind to DNA, obscuring activation domains or hindering interactions with basal transcriptional machinery or co-factors. Additionally, GR may recruit histone deacetylases (HDACs) to such complexes, increasing chromatin condensation, restricting access by transcriptional machinery and thereby reducing transcription (Hua, Ganti, & Chambon, 2016; Hua, Paulen, & Chambon, 2016; Newton, 2014).

In transactivation, glucocorticoid-bound GR binds to GREs present in DNA, enhancing associated gene expression (Newton, 2014; Vandevyver et al., 2013). Many of the genes induced have anti-inflammatory activity and contribute to the significant post-transcriptional repression of inflammatory protein production mediated with glucocorticoid treatment (Fan et al., 2006; Ing, 2005; Newton, 2014; Newton, Staples, Hart, Barnes, & Bergmann, 2001). ICS-inducible genes also repress inflammatory pathways, with cyclin-dependent kinase inhibitor 1C (CDKN1C) and dual specificity protein phosphatase 1 (DUSP1/MKP1) suppressing inflammatory mitogen-activated protein kinase (MAPK) pathways, while TSC22 domain family protein 3 (TSC22D3/GILZ) attenuates NF-κB and AP-1 activity (Ayroldi & Riccardi, 2009; Chang et al., 2003; King, Holden, Gong, Rider, & Newton, 2009; Mittelstadt & Ashwell, 2001; Newton, 2014). Indeed, many genes with potentially anti-inflammatory activity are induced in the lungs of healthy and asthmatic volunteers after glucocorticoid inhalation (Kelly et al., 2012; Leigh et al., 2016). Factors reducing glucocorticoid-inducible gene expression, therefore, have the potential to contribute to resistance (Klaßen et al., 2017; Newton et al., 2017; Rider, King, Holden, Giembycz, & Newton, 2011).

2.3. Air pollution

Everyone is routinely exposed to myriad substances in their environment, through routes including contact, ingestion, and inhalation (Moya, Bearer, & Etzel, 2004). In the context of lung diseases, such as asthma, the most important route for environmental exposures is through inhalation. Air pollution is typically composed of multiple small components, including organic chemicals, metals and adherent biological materials, such as allergens; elements of this mixture are broadly categorized within either the solid (particulate matter (PM)) or gaseous fraction (Reşitoğlu, Altinişik, & Keskin, 2015; Wichmann, 2007). Chemical air pollutants include simple molecules such as carbon monoxide (CO), nitrogen oxides (NO_x), sulphur dioxide (SO_2) and ozone (O_3), and more complex entities, including a variety of polycyclic aromatic hydrocarbons (PAHs) (Reşitoğlu et al., 2015). Airborne PM can originate from natural sources, such as wind-blown soil or sea spray, or be generated by abrasive processes, such as braking or car tires rubbing on the pavement, or be produced by the combustion of fossil or biomass fuels (Kelly & Fussell, 2015). Many studies of air pollution have used diesel exhaust (DE) and diesel exhaust particles (DEP), produced by the diesel engines used in generators and vehicles, as paradigmatic of combustion. DEPs mostly consist of carbon cores to which a variety of molecules including PAHs and allergens can attach (Kagawa, 2002; Nightingale et al., 2000; Riedl & Diaz-Sanchez, 2005). DE contains particles smaller than 10μm (PM_{10}) and 2.5μm ($PM_{2.5}$), but the vast majority of particles are usually ultrafine ($PM_{0.1}$), which have relatively high penetration into the distal lung by diffusion. Smaller particles not only deposit in the lungs, but may enter the bloodstream and even the brain, either via the circulatory system, after phagocytosis by antigen presenting cells or directly through the nasal olfactory mucosa and the olfactory bulb (Babadjouni et al., 2017; Costa et al., 2014).

Increasing awareness of the harmful effects of air pollution on health has led to the development of emission standards, which are focused on setting maximum allowable concentrations, over various durations, for specific air pollutants (Mayerhofer et al., 2002). For example, the World Health Organization (WHO) ambient air quality guidelines recommend that individuals are not exposed to $PM_{2.5}$ levels exceeding an annual mean of 10 $\mu g/m^3$, or a 24-h mean of 25 $\mu g/m^3$ and PM_{10} levels of 50 $\mu g/m^3$ over 24 h or 20 $\mu g/m^3$ annually (World Health Organization, 2016). However, there is no evidence of a safe level of exposure, and air pollution concentrations regularly exceed guideline levels in many regions. In nations where there are no, or weak, air quality regulations, rapid development often results in human populations clustered in areas with high air pollution (Colvile, Hutchinson, & Warren, 2002; Faiz & De Larderel, 1993; Shea, Truckner, Weber, & Peden, 2008). For example, Beijing had annual mean $PM_{2.5}$ levels in excess of 85 $\mu g/m^3$ in 2013, while maximal concentrations in areas of China and India occasionally exceed 700 $\mu g/m^3$ (Kelly & Fussell, 2015; Xu et al., 2016). Unfortunately, high levels of air pollution are common and even in 2016 over 92% of people worldwide were exposed to air pollution that exceeded WHO $PM_{2.5}$ limits (Kirby, 2016; World Health Organization, 2016). Low- and middle-income cities are particularly affected, with 98% of those with populations exceeding 100,000 having levels that do not meet the WHO guidelines.

2.4. Health effects of air pollution exposure

A detailed description of the many health effects of air pollution, from both natural and anthropogenic sources, is outside the scope of this review. Instead, we would direct readers to a number of excellent recent reviews (Cohen et al., 2017; Landrigan et al., 2018; Wu, Jin, & Carlsten, 2018). Outdoor air pollution exposure is estimated to be responsible for ~3 million deaths worldwide, with a further 3.5 million attributable to indoor air pollution (World Health Organization, 2016). For example, in areas of northern China, air pollution exposure has become the top risk factor associated with early death (Xu et al., 2016). Additionally, air pollution has significant effects on morbidity, contributing to an estimated 85 million DALYs. The most significant effects of air pollution are thought to be on cardiovascular conditions, lung diseases, and cancer, but exposure can also affect cognitive function and pregnancy (Curtis, Rea, Smith-Willis, Fenyves, & Pan, 2006). PM size appears to affect health outcomes, with fine PM that can penetrate deep into the lungs generally associated with greater harm than coarse PM (Valavanidis, Fiotakis, & Vlachogianni, 2008). The composition of PM also appears to affect health outcomes, with, endotoxin, organic and especially transition metal constituents associated with higher toxicity (Strak et al., 2012; Valavanidis et al., 2008).

There is considerable evidence demonstrating that air pollution exacerbates and even contributes to the development of asthma (Bowatte et al., 2015; Zheng et al., 2015). Asthma diagnosis is much higher in urban areas, relative to rural settings (Zhu et al., 2015). There are a number of factors associated with urban living that may contribute to this trend, including greater exposure to air pollution (Byrd & Joad, 2006; Jie, Isa, Jie, Ju, & Ismail, 2013). Sudden rises in air pollution,

for example from forest fires, decrease asthma control and increase emergency room visits, hospitalization and bronchodilator use (Henderson, Brauer, MacNab, & Kennedy, 2011; Henderson & Johnston, 2012). Non-anthropogenic PM found in rural environments, including desert sand and windblown dust, have also been shown to increase the incidence of asthma exacerbations and hospitalization (Gupta, Singh, Kumar, Choudhary, & Singh, 2012; Kanatani et al., 2010; Strak et al., 2012; Yitshak-Sade et al., 2015). One factor potentially contributing to the enhanced risk of asthma exacerbation following air pollution exposure is the induction of glucocorticoid resistance.

2.5. Glucocorticoid resistance

Glucocorticoids are ineffective in some asthmatics, particularly those with severe disease, or following exposures to respiratory viruses or cigarette smoke (Hansbro et al., 2017; Holgate & Polosa, 2006; Poon, Eidelman, Martin, Laprise, & Hamid, 2012). There are a number of different definitions, but glucocorticoid resistance can be clinically defined as a lack of improvement in forced expiratory volume in one second (FEV_1) following one to two weeks of treatment with an oral corticosteroid, at a dose equivalent to 40 mg of prednisolone daily (Barnes, Greening, & Crompton, 1995; Keenan et al., 2012). This definition sidesteps some of the issues inherent with ICS use, where reports indicate that the majority of asthmatics have poor inhaler technique, often leading to reduced doses and inadequate disease control (Giraud & Roche, 2002; Haughney et al., 2008). Resistance can also be defined as a decrease in maximal response, which may be described as glucocorticoid hypo-responsiveness; but the term resistance is also often used in situations where a degree of insensitivity exists that can be entirely overcome with an increase in dose (Keenan et al., 2012). Unfortunately, those with resistance, who do not receive many benefits from their medications, are often still vulnerable to the side effects of glucocorticoids (Carmichael et al., 1981; Keenan et al., 2012).

Glucocorticoid resistance can be genetically mediated through mutations of the glucocorticoid receptor, such as in familial glucocorticoid resistance or Chrousos syndrome, but the number of asthmatics affected in this way is probably small (Charmandari et al., 2005; Chrousos et al., 1982; Yang, Ray, & Matthews, 2012). Instead, glucocorticoid resistance may be transiently induced by viral infections, or maintained over longer timeframes in severe asthma and asthmatics who smoke (Hansbro et al., 2017; Keenan et al., 2012; Poon et al., 2012). Reversing resistance in those with severe asthma may be difficult to achieve, but any progress would be very impactful as this population incurs substantial healthcare costs (Bahadori et al., 2009; Hansbro et al., 2017).

The number of asthmatics who are genuinely glucocorticoid-resistant is thought to be in the range of 0.01-0.1%, but the proportion in which temporary resistance or insensitivity can be induced is probably much larger, encompassing moderate and even mild asthmatics who occasionally experience exacerbations (Trevor & Deshane, 2014; Yim & Koumbourlis, 2012). Mild asthmatics are likely to have their infrequent exacerbations induced in conjunction with upper respiratory tract infections (Jackson & Johnston, 2010; Proud, 2011). Therefore, studies focusing on this population potentially underemphasize the effects of other environmental factors, such as air pollution. The majority of asthma exacerbations in a US population, which may be triggered by environmental factors including air pollution exposure, were experienced by mild (Global Initiative for Asthma (GINA) Step 1 & 2) asthmatics (56%) in a study by Suuki *et al.* (Global Initiative for Asthma, 2017; Suruki, Daugherty, Boudiaf, & Albers, 2017). This was because the number of mild asthmatics was substantially higher than that of severe asthmatics (GINA Step 5), who only represented 8% of exacerbations. Indeed, mild and moderate asthmatics (GINA Steps 1-3) experienced 73% of asthmatic exacerbations in this study. Nevertheless, only 11% of mild-moderate asthmatics experienced an exacerbation within a 1 year period, compared to 30% of severe asthmatics (Suruki et al., 2017).

Many studies have demonstrated that cigarette smoking can also contribute to asthma exacerbation incidence, in addition to being a key driver of lung cancer and chronic obstructive pulmonary disease (COPD) development (Pattenden et al., 2006; Piipari, Jaakkola, Jaakkola, & Jaakkola, 2004; Stapleton, Howard-Thompson, George, Hoover, & Self, 2011). Surprisingly, data suggest that approximately 20% of asthmatics smoke, a proportion equivalent to, or maybe even higher than, that of the general population (To et al., 2012; US Centers for Disease Control and Prevention, 2017). Cigarette smoking appears to induce resistance in asthmatics and probably underlies the intrinsic glucocorticoid insensitivity of COPD (Barnes, 2013; Livingston, Thomson, & Chalmers, 2005; Stapleton et al., 2011). Cigarette smoke exposure has nevertheless also been shown to enhance the production of the endogenous glucocorticoid cortisol (Badrick, Kirschbaum, & Kumari, 2007; Wilkins et al., 1982). Cigarette smoke consists of gases and PM and has many features in common with other forms of air pollution, such as DE, including inducing endogenous glucocorticoid production. However, the effects of endogenous glucocorticoid release on glucocorticoid resistance remain unclear.

3. Effects of air pollution on glucocorticoid release

3.1. Air pollution-induced corticosterone production

Recent animal studies have suggested that exposure to air pollution increases blood concentrations of corticosterone, the primary endogenous glucocorticoid in rodents (Jia et al., 2018; Thomson et al., 2016; Thomson, Vladisavljevic, Mohottalage, Kumarathasan, & Vincent, 2013). However, a significant caveat in all studies measuring serum glucocorticoids is that any stress is likely to induce endogenous glucocorticoid release, making the inclusion of appropriate controls vital. Significantly increased plasma concentrations of corticosterone were observed in mice breathing ambient air from outdoors (91.3 $\mu g/m^3$ of $PM_{2.5}$ mean concentration) versus those exposed to high-efficiency particulate air (HEPA) filtered ambient air (17.9 $\mu g/m^3$ of $PM_{2.5}$) over 140 days (Jia et al., 2018). A study by Martrette et al. also demonstrated that corticosterone levels were increased by 2-fold in female rats following exposure for 6 hours a day over 15 days to 0.12 ppm O_3, as compared to control rats in the same room breathing charcoal-filtered air continuously (Martrette, Thornton, & Trabalon, 2011). Similarly, a study with male Fisher-344 rats indicated that acute exposure for 4 h to 0.8 ppm O_3 was associated with a 2-fold increase in plasma corticosterone levels. Such increased blood corticosterone concentrations were dose-dependently reduced by prior treatment with metyrapone, which inhibits the enzyme catalyzing the final step in glucocorticoid synthesis steroid 11β-hydroxylase (Thomson et al., 2016). However, treatment with O_3 or metyrapone did not affect plasma epinephrine levels. But blocking corticosterone production with metyrapone increased expression of inflammatory proteins in the lungs and blood, suggesting that the endogenous glucocorticoid was acting to reduce local and systemic inflammation (Thomson et al., 2016).

A study in male rats demonstrated that exposure to PM concentrated from the ambient local air (~500 $\mu g/m^3$ of $PM_{2.5}$) for 8 hours significantly increased serum corticosterone at 24 h (Sirivelu, MohanKumar, Wagner, Harkema, & MohanKumar, 2006). In pregnant female rats exposed to DE, or particle-filtered DE (i.e. the gaseous fraction), corticosterone levels were likewise significantly increased, relative to filtered air (Li et al., 2013). However, *in utero* exposure to either DE or filtered DE appeared to significantly decrease serum corticosterone concentration as measured in male rats on postnatal day 28, suggesting sustained effects potentially through a long-lasting epigenetic mechanism, such as DNA methylation (Li et al., 2009).

3.2. Effects of combined exposures on corticosterone release

Increased corticosterone was also induced by acute ozone (0.8 ppm) or particulate matter (50 mg/m^3) inhalation, as compared to filtered air,

in male Fisher-344 rats, in a manner that correlated with increased ACTH (Thomson et al., 2013). Furthermore, corticosterone levels were additively increased in rats exposed to both O_3 and PM. Likewise, in rats pre-sensitised over three days with intranasal instillation of 0.5% ovalbumin (OVA), an allergen found in egg white, intranasal instillation of 1% OVA in addition to concentrated ambient PM (500 μg/m^3 $PM_{2.5}$) exposure further enhanced serum corticosterone levels, relative to saline and filtered air controls (Sirivelu et al., 2006). This result suggests that combined exposures to air pollution and allergens, as are frequently encountered in cities where there is traffic, plants and trees, may further enhance endogenous glucocorticoid release (Carlsten & Rider, 2017).

Data showing increased release of corticosteroids and adrenaline following exposure to O_3 are supported by a study in which Wistar-Kyoto rats underwent bilateral adrenal demedullation (elimination of the adrenal gland tissue producing adrenaline and noradrenaline), total bilateral adrenalectomy (removal of the adrenal glands) or a sham surgery (Miller et al., 2016). After 4 days of recovery, the rats were exposed to either air or 1 ppm of ozone for 4 h on one or two days. Ozone exposure enhanced the plasma concentration of corticosterone in rats that underwent sham surgery, while demedullation decreased corticosterone levels by about 40% and adrenalectomy abolished expression. Likewise, O_3 exposure enhanced adrenaline release in the rats who had sham surgery, but adrenaline expression was abrogated by both demedullation and adrenalectomy. Furthermore, O_3 exposure-induced bronchioalveolar lavage (BAL) neutrophilia, lung protein leakage and glucose intolerance in sham-treated rats, was not found in rats subjected to demedullation or adrenalectomy. O_3 exposure also increased enhanced pause (Penh) by up to 4 fold in rats that underwent either sham or demedulation surgery, but this was significantly reduced by ~50% following adrenalectomy (Miller et al., 2016). These results suggest that adrenaline release induced by O_3 exposure enhances lung neutrophilia and glucose intolerance, while corticosterone production may affect breathing. However, effects due to other factors produced by the adrenal gland cortex or medulla cannot be ruled out.

3.3. Effects of air pollution-induced corticosterone release

A study by Clougherty *et al.* showed that Sprague-Dawley rats stressed by spending time in the home cage of a dominant male had enhanced inflammatory responses to concentrated ambient PM exposure (Clougherty et al., 2010). Rats exposed to both stress and PM for 5 hours a day over ten days had increased white blood cell counts, tumor necrosis factor α (TNFα) and C-reactive protein levels, relative to those only exposed to particles. The authors suggest that these effects result from increased activation of the HPA and sympathetic-adrenal-medullary axes and subsequent cortisol release.

3.4. Air pollution-induced cortisol release in humans

There is emerging evidence for increased blood cortisol levels in humans following air pollution exposure. Jia *et al.* performed a natural experiment with 12 non-smoking adult males living in Beijing, from whom blood was collected after a week of low air pollution in December 2013 (mean 47.6 μg/m^3 $PM_{2.5}$) and another with high air pollution (mean 276.9 μg/m^3) in February 2014 (Jia et al., 2018). Cortisol concentrations were significantly increased in plasma samples taken after the week of high air pollution, relative to the week of lower levels. Likewise, a study comparing municipal police employees who worked indoors or outside, in a city in Italy with pollution levels of 30-60 μg/m^3 of PM_{10}, showed that those officers working outdoors who did not smoke had significantly higher cortisol levels than those working indoors (Tomei et al., 2003). However, obvious confounding factors in these unblinded studies includes the exact nature of the work and the knowledge that one is exposed to high air pollution may be a source of psychological stress (Clougherty & Kubzansky, 2009).

Nevertheless, further support for pollution-induced increases in endogenous corticosteroids comes from a well-controlled and blinded recent study conducted in Shanghai, China (Li et al., 2017). This study employed a controlled crossover design with a working or sham air filter placed in the middle of a college dormitory for nine days in a randomized order, with a 12-day washout between the study arms. Mean time-weighted personal $PM_{2.5}$ exposures were calculated to be 53.1 μg/m^3 with the sham air filter but decreased to 24.3 μg/m^3 during the period when the high-efficiency air filter was present. This study indicated that serum levels of the glucocorticoids cortisol and cortisone were significantly increased by 1.33 and 1.18 fold respectively during the sham periods. Concentrations of the catecholamines epinephrine and norepinephrine were also increased by 1.2 and 1.57 fold respectively. The authors estimated that cortisol levels were increased by ~8% for every 10 μg/m^3 increase in $PM_{2.5}$ concentration. Serum concentrations of glucose and glucose 6-phosphate were also significantly increased by higher $PM_{2.5}$ concentrations (Li et al., 2017).

3.5. Summary of the effects of air pollution on glucocorticoid release

Together these studies indicate that exposure to different types of air pollution, including PM and O_3, either alone or in combination enhance corticosterone release in rodents and cortisol in humans. Corticosterone release may be potentiated by exposure to an allergen in addition to air pollution and appears to have long-term epigenetic effects in rodents. Corticosterone production following air pollution exposure may act to reduce local and systemic inflammation, but is also associated with enhanced lung neutrophilia, protein leakage and glucose intolerance. Stress responses appear to induce HPA activation with the subsequent release of glucocorticoids and other stress hormones, independent of any effects of air pollution. Indeed, stress may actually induce glucocorticoid resistance (Miller, Gaudin, Zysk, & Chen, 2009; Wright, 2009). However, to the best of our knowledge, no study has evaluated the effects of acute exposure to controlled concentrations of diesel exhaust on glucocorticoid resistance, in a well-blinded crossover study.

4. Epidemiology of air pollution and the effects of glucocorticoids

4.1. Air pollution, cigarette smoke and glucocorticoid resistance

Cigarette smoke and environmental air pollution share similarities in composition, toxicity and health effects (Bhalla, 2002; De Marco et al., 2016; Fetterman, Sammy, & Ballinger, 2017; Middlekauff, Park, & Moheimani, 2014; Pope & Dockery, 2006; Reid et al., 2016). Both cigarette smoke and traffic-related air pollution are composed of a complex mixture of gases and particulate matter (Fetterman et al., 2017). There is ample evidence that cigarette smoke contributes to glucocorticoid resistance in asthma and COPD (Barnes, 2013; Livingston et al., 2005; Spears et al., 2013; Stapleton et al., 2011). Given the similarity between cigarette smoke and other types of air pollution, including traffic-related air pollution (TRAP), there is clear plausibility for other types of air pollution, such as TRAP, to contribute to glucocorticoid insensitivity. Indeed, a recent study demonstrated the induction of glucocorticoid resistance in a mouse model of asthma following exposure to diesel exhaust PM (Brandt & Hershey, 2016). A number of other papers have suggested, albeit tangentially, that air pollution may contribute to glucocorticoid resistance in asthmatics (Hansbro et al., 2017; Holgate & Polosa, 2006; Matsui, 2014). Nevertheless, the evidence for environmental air pollution-induced glucocorticoid resistance in humans is very limited, at this point consisting of studies showing association (Table 1). Before describing these studies in more detail, we wish to suggest some reasons for this modest literature.

Assessment of glucocorticoid resistance takes time as definitions generally require repeated spirometry testing of individuals over a

period of one to two weeks, to consistently demonstrate a lack of response to a high dose glucocorticoid (Barnes et al., 1995; Keenan et al., 2012). Such testing is laborious, costly and limited by risks, including that of developing side effects from the oral glucocorticoid. Epidemiological observations on the other hand rarely include controlled interventions. Furthermore, unlike studying the effects of cigarette smoke where smokers and non-smokers will inevitably have large asymmetry in exposures, asthmatics within the same region face less extreme variation in concentrations of air pollution; there may be small local dissimilarity due to 'hot spots', but differences in air pollution exposure within a local population over time are infrequently different by multiple orders of magnitude (Fujita, Campbell, Arnott, Johnson, & Ollison,

Table 1
Summaries of epidemiological studies on air pollution and corticosteroids. This table provides summary details of studies described in Section 3, including the first author and year of each study, demographic details for study volunteers, medications and details of results. ≈, correlated with; ↓, decreased; ↑, increased. For concentrations of air pollutants in these studies please see online Supplemental 1.

First author, year	Number of volunteers	Mean age (years)	Female (%)	Medications	Changing medication use	Spirometry effects	Asthma symptoms
Delfino et al. (1998)	24	12.9	38	33% on non-steroidal controller, 25% on ICS			↑ PM_{10} (lag 0/5 day mean) or O_3 (lag 0) ≈ ↑ symptoms in those on no med, compared to anti-inflammatory
Delfino et al. (2002)	22	14	36	27% on ICS, 18% on cromolyn or nedocromil			↑ PM_{10} (3 day mean) ≈ ↑ Asthma Symptoms, in those not on medications
Delfino et al. (2006)	45	13.5	31	46% on ICS or ICS plus antileukotriene			↑ $PM_{2.5}$ or NO_2 ≈ ↑ eNO, greater in ICS, reduced in ICS plus anti-leukotriene
Desqueyroux et al. (2002)	60	55	62	100% on ICS, 20% on OCS			↑ PM_{10} (lag 4-5) or O_3 (2 d) ≈ asthma exacerbations, no difference in ± OCS
Dusseldorp et al. (1995)	32	47	66	72% on bronchodilators, 78% on maintainance medications, 28% smokers	↑ PM_{10} (lag 2) ≈ ↑ increased maintainance medication use. ↑ PM_{10} (lag 0, 1 & 3) ≈ ↑ bronchodilator use.		
Hiltermann et al. (1998)	60	31	45	85% on bronchodilator, 75% on ICS	↑ O_3 and PM_{10} (7 day means) ≈ ↑ bronchodilator use.	Air pollution increases not associated with PEF (confounded by meds?).	↑ O_3, PM_{10} and NO_2 ≈ ↑ shortness of breath. No difference between those on high or low dose ICS.
Ierodiakonou et al. (2016)	1003	9	40	Children randomised to placebo, ICS or nedocromil		↑ O_3 ≈ ↓ lung function, stronger in those on ICS. ↑ CO (mean concentration 1μg/m^3) (lag 0, 1 week mean) ≈ ↓PC_{20}, in groups on ICS or nedocromil.	
Jacquemin (2012)	481	39.5	49.7	49% on ICS	Greater ICS use in partly controlled and uncontrolled asthma.		↑ PM_{10} and O_3 ≈ ↓ asthma control, not modified by ICS. Trend towards increased sensitivity to O_3 in those on ICS.
von Klot et al. (2002)	53	59.0	62	83% on ICS, 79% on SABA, 15% on OCS	↑ $PM_{2.5}$ (5 and 14 day mean) ≈ ↑ increased corticosteroid use. ↑ $PM_{2.5}$ (5 day mean) ≈ ↑ SABA use.		↑ $PM_{2.5}$ ≈ ↑ Asthma Symptoms
Koenig et al. (2003); Koenig et al. (2005)	19	9	26	47% on ICS		↑ $PM_{2.5}$ ≈ ↑ eNO, in no med, no effect in those on ICS	
Lewis et al. (2005)	86	9.1	43	ICS, non-steroidal controller, SABA		↑ PM_{10} or O_3 (lag 2) ≈ ↓ FEV_1, in those on ICS	
Lewis et al. (2013)	298	8.9	42	9.7% on ICS, 13.1% on non-steroidal controller, 43.3% on SABA, 33.9% on no meds		↑ $PM_{2.5}$ (lag 2, 5 day mean) or O_3 (3-5 and 5 day mean) ≈ ↑ wheeze and shortness of breath, in those on ICS.	
Li et al. (2009)	182	11	37	37% on ICS, 35% on SABA, 18% on other, 42% no meds		↑ SO_2 or $PM_{2.5}$ ≈ ↓ FEV1, only in those not on ICS.	↑ O_3 (lag 0, 2 day mean) ≈ ↓ FENo, no difference between those on and not on ICS.
Mortimer et al. (2000)	846	~7	37	15% on no meds, 42% on bronchodilators, 10% on cromolyn, 34% on ICS		↑ O_3 ≈ ↓ PEF, greater in those on no med than in those on ICS in premature or low birthweight. Greater in Cromolyn in normal births.	↑ O_3 ≈ ↑ Asthma Symptoms, in those on no med
Pope et al. (1991)	21	28.7	52		↑ PM_{10} ≈ ↑ extra medication usage		
Qian et al. (2009)	119	~30	69	Randomization to placebo, LABA or ICS			↑ NO_2 ≈ ↑ eNO in ICS and LABA users. ↑ PM_{10} ≈ ↑ eNO in LABA, but not ICS users.
Rabinovitch et al. (2006)	73	10.4	NR	78% on ICS, SABA doses recorded	↑ SABA use in severe asthma group, as compared to moderate.		
Silverman et al. (1992)	30	48	73	Xanthenes, ICS and SABA.	↑ PM_{10} ≈ ↓ FEV_1 in Summer, increased FEV_1 in Winter		

2014). Exposure to cigarette smoke generally only occurs in the houses of smokers in countries with public smoking laws, but concentrations of PM and gases experienced by smokers are certainly orders of magnitude higher than the WHO recommended limits on environmental air pollutants (De Marco et al., 2016; Invernizzi et al., 2004; World Health Organization, 2016). For example, a comparison of smoke from three cigarettes and a diesel car running in a small (60 m^3) enclosed space showed $PM_{2.5}$ levels of 319 and 31 μg/m^3 respectively (Invernizzi et al., 2004). Nevertheless, data suggests that even exposure to secondhand smoke, which is likely to be at lower concentrations, can contribute to glucocorticoid resistance (Halterman et al., 2004). Effects at lower concentrations may reflect a non-linear dose-response curve for adverse effects of PM, albeit best documented for chronic phenomena (Pope et al., 2009).

There are a few ways to circumvent issues of air pollution concentration and exposure time, for example by performing controlled exposures using purpose-built facilities or through monitoring air pollution fluctuations in an area over time (Birger et al., 2011; Jia et al., 2018; Pope, Dockery, Spengler, & Raizenne, 1991). However, few facilities exist, and there are blinding, ethical, time and expense issues with performing controlled exposures in volunteers for more than a few hours to concentrations of air pollution substantially above ambient levels. Likewise, epidemiological studies monitoring air pollution levels over time have historically been limited by the sparse geographical distribution of air pollution monitors (Marshall, Nethery, & Brauer, 2008; Snyder et al., 2013). Furthermore, the effects of air pollution may take time to result in chronic inflammation, asthma symptoms and glucocorticoid resistance, meaning that analysis over short time periods may miss significant correlations (Peters, Dockery, Heinrich, & Wichmann, 1997). Regardless, epidemiological studies have substantial value in highlighting a possible relationship between air pollution exposure and glucocorticoid responses, as detailed in the following sections.

4.2. Association of medication usage with air pollution

One potential signal of changing glucocorticoid response is fluctuations in the control of asthma symptoms with a given medication dosage. Reduced symptom control may also lead to increased medication usage. Indeed, studies suggest that there is increased medication use among asthmatics during periods of higher air pollution. One of the first air pollution epidemiology studies was conducted by Pope III *et al.* focusing on the effects of exposure to PM_{10} in Utah Valley in the early 1990's (Pope et al., 1991). The principal source of air pollution in this community was an integrated steel mill, which the authors suggest produced 50-70% of PM_{10} emissions in the valley, with 24-h recording at three sites which ranged from 11-195 μg/m^3 (mean of 46 μg/m^3). They recruited two volunteer populations, the first consisting of children aged 9-11 with asthma and the second of individuals aged 8-72 receiving medical treatment for asthma. Volunteers were given peak flow meters for use at home and recorded asthma symptoms, peak expiratory flow (PEF), and medication use, nightly. The results indicated a significant positive correlation between higher levels of air pollution, decreased PEF, increasing asthma symptoms and extra (in addition to regular) asthma medication use. By breaking the 24-hour PM_{10} levels into three ranges (0-50, 51-100 and 101-200 μg/m^3) they showed a stepwise decrease in PEF and an increase in extra medication use with higher concentrations in both study populations (Pope et al., 1991). Nevertheless, the authors did not define 'asthma medications' or provide a breakdown of the classes used, and therefore effects on glucocorticoid use specifically are unclear in this study, particularly since 'extra' medication use predominantly means bronchodilators in these scenarios.

There are other challenges in epidemiological studies seeking to investigate effects on maintenance medications. Prescriptions for maintenance medications, such as ICS, encourage consistent daily use, making it difficult to demonstrate changes in usage due to exposures in those not instructed to increase medication doses in response to symptoms (von Klot et al., 2002). Errors can be further compounded by inaccurate reporting by volunteers. Furthermore, in observational studies, it may be onerous to distinguish between the need for more medications due to increased bronchoconstriction or inflammation and psychological factors, such as anxiety, in response to perceived increases in air pollution. While such anxiety may be addressed by surveys if volunteers are conscious of this fear, data has shown that perception can substantially affect symptoms reported on surveys (Carlsten et al., 2013).

4.3. Association of corticosteroid usage with air pollution

A number of studies have nevertheless demonstrated an association between air pollution exposure and increased maintenance medication use (Table 1). For example, a study conducted in Germany during the winter of 1996-1997, demonstrated a strong correlation between 14-day trends for fine and ultrafine PM and glucocorticoid use (von Klot et al., 2002). In this study non-smoking asthmatic volunteers kept daily health status and medication use dairies, which were compared with PM concentrations in the range 0.01-2.5 μm recorded in 10-minute intervals using a mobile aerosol spectrometer, with SO_2 (same site), NO_2 and CO (regional recorders) concentrations also documented. Study results indicated an association between the 5-day (but not same day) mean air pollution level and β_2-adrenoceptor agonist use. Correlations were also demonstrated between same-day exposure to the gases NO_2 or CO and increased glucocorticoid use (von Klot et al., 2002). Interestingly, there were differences between the effects of specific air pollution components on symptoms, with the concentrations of the gases NO_2 and CO correlated with wheeze, but no association with PM.

A later study also found significant increases in $PM_{2.5}$ concentration correlated with increased bronchodilator usage, despite 78% of the children studied taking ICS at unspecified dosages (Rabinovitch, Strand, & Gelfand, 2006). A study conducted in the Netherlands with 32 adult asthmatics had similar findings for bronchodilators and also identified a significant effect of maintenance medications (Dusseldorp et al., 1995). PM_{10} levels were correlated with increased same-day, lag 1- and lag 3-day bronchodilator use and with lag 2-day maintenance medication use (ICS, long-acting β2-adrenoceptor agonist (LABA), cromoglicate, and nedocromil were not separately reported). Interestingly, those with worse symptoms on recruitment appeared to be most affected by PM_{10} exposure. Likewise, the nine smokers in the study seemed particularly susceptible to air pollution, rather than having smoking overwhelm any effects of exposure to comparatively modest air pollution concentrations (Dusseldorp et al., 1995).

Similar results were obtained in a study that evaluated the response to summer air pollution (mean O_3 and PM_{10} of 80.1 and 39.7 μg/m^3 respectively) in adults with mild-severe asthma, 75% of whom were taking ICS (Hiltermann et al., 1998). They found a significant correlation between same day O_3 levels or 7-day PM_{10} levels and bronchodilator use. A 'significant' relationship was also found between ICS use and prior day black smoke levels (at $p < 0.1$), with a similar trend for PM_{10} exposure. Increases in O_3, NO_2 and coarse PM exposure were associated with increased shortness of breath. However, there were no significant differences in symptoms in response to O_3 in those using high versus low (<400 μg) ICS doses or by PC_{20}. Likewise, Desqueyroux *et al.* showed that even treatment with high dose oral corticosteroids, in an asthma cohort with everyone on ICS, did not modify the association between higher PM_{10} or O_3 exposure and an increased exacerbation frequency (Desqueyroux, Pujet, Prosper, Squinazi, & Momas, 2002). Hence, asthma severity as assessed by PC_{20} or corticosteroid dose was not a useful marker of response to air pollution, but rather individual susceptibility appeared to be the most significant driver of symptoms.

A role for individual susceptibility, without modification by ICS, was also shown in an extensive study conducted by Jacquemin *et al.* on 481 volunteers in 5 French cities (Jacquemin et al., 2012). This study

evaluated the effects of long-term O_3 and PM_{10} exposure in a population that had differing degrees of asthma control, with 44% controlled, 29% partly-controlled and 27% uncontrolled. They found an association between increased long-term exposure to O_3 and/or PM_{10} and decreased symptom control that was maintained even after adjustment for environmental tobacco smoke exposure and ICS use (Jacquemin et al., 2012). These results suggest that taking a corticosteroid, whether at a high dose or low, may not reduce the need for bronchodilators or modify symptoms in response to air pollution, indicating a possible role for ICS insensitivity.

4.4. Beneficial effects of ICS treatment in response to air pollution

There are also data indicating protective effects of ICS in asthmatics exposed to air pollution (Table 1). For example, in a study by Delfino *et al.* anti-inflammatory medications appeared to reduce symptoms, in comparison to bronchodilators, induced by PM_{10} or O_3 exposure (Delfino, Zeiger, Seltzer, & Street, 1998). This study focused on air pollution in a southern California community in an air inversion zone. A total of 25 asthmatics aged 9-17 recorded symptoms and medication use each night between August and October 1995. Asthma symptoms correlated with PM_{10} and O_3 levels, alone and in co-exposure models, over various time frames, including 1, 8 and 24 h. Stronger effects were seen for PM_{10} than O_3, with only weak correlation seen between these two pollutants. Children taking anti-inflammatory medications had significantly reduced symptoms compared to those only taking bronchodilators in response to PM_{10} and O_3, both as mono-exposures and in combination, over most of the time frames measured. Similar results were obtained in a follow-up study by the same group that was performed in spring, rather than fall, and had lower mean pollution levels (Table 1) (Delfino, Zeiger, Seltzer, Street, & McLaren, 2002). This showed an association between increased PM_{10} and asthma symptoms, in those not on either ICS, cromolyn or nedocromil. Potentially this reflected reduced inflammation, as ICS also appeared to reduce exhaled nitric oxide (eNO), a marker of lung inflammation previously associated with $PM_{2.5}$ exposure in mild to moderate asthmatic children (Koenig et al., 2003), with repeated analysis (Koenig et al., 2005; Mar et al., 2005).

Other studies have shown protective effects of ICS on PEF and FEV_1 spirometry values (Table 1). Mortimer *et al.* performed a large cohort study of mild to severe asthmatics to determine whether air pollution exposure had differing effects in children who were born prematurely or had low birth weight (Mortimer, Tager, Dockery, Neas, & Redline, 2000). They found an association between 8-hour O_3 exposure and asthma symptoms only in those children not on any medications. Taking an ICS rather than no medications appeared to reduce the decline in PEF associated with increased O_3 exposure in children born prematurely or with low birthweight. ICS also appeared to prevent a decrease in FEV_1 associated with increased $PM_{2.5}$ or SO_2 exposure in children with mild to moderate asthma (Liu et al., 2009). Together these results suggest that taking an ICS maintenance medication may reduce some of the harmful effects of air pollution exposure.

Studies have nevertheless shown that the bronchodilators volunteers enrolled in such studies take may be effect-modifying, or even confounding, in the association between asthma and air pollution, by increasing apparent lung function despite high levels of air pollution. For example, Silverman *et al.* measured exposure using personal monitoring systems that recorded PM, SO_2, and nitrogen dioxide (NO_2) and evaluated the effects of PM on PEF and composite medication use (Silverman, Hosein, Corey, Holton, & Tarlo, 1992). Interestingly, they saw evident seasonal effects, with a decrease in FEV_1 and forced vital capacity (FVC) with increasing PM in summer, but an increase in pulmonary function with increasing air pollution in winter. They state that the winter effects are likely due to confounding by greater medication use, possibly in response to lower temperatures, leading to improved spirometry despite the PM present; although seasonal reductions in aeroallergens could be an additional unmeasured confounder (Buckley & Richardson, 2012; Zhang et al., 2014).

4.5. Harmful effects of asthma medications?

A recent extensive study conducted in 8 large North American cities (Albuquerque, Baltimore, Boston, Denver, San Diego, Seattle, St Louis, Toronto) suggested that maintenance medications may enhance the harmful effects of air pollution on lung function and PC_{20} in mild to moderate asthmatics (Ierodiakonou et al., 2016). The authors correlated levels of O_3, CO, NO_2 and SO_2 at residence postal codes, with FEV_1, FVC, and PC_{20} measured during repeated visits between December 1993 and June 1999, in 1003 asthmatic children randomized to treatment with placebo, the ICS budesonide or nedocromil. Day and week CO concentrations were associated with modest, but significant decreases in postbronchodilator FEV_1 (0.5 ppm increase in same-day CO reduced FEV_1 by 0.3%) and FVC. Surprisingly, budesonide significantly enhanced CO-mediated reductions in FEV_1. Four-month NO_2 concentration was also associated with a decrease in FVC and this was significantly augmented by nedocromil. Nedocromil also had greater negative effects than budesonide on PC_{20} in association with CO exposure. Nevertheless, the analyses of variance (ANOVAs) used to determine the interactions of individual gases with these maintenance medications were not significant. Additionally, the authors of this study suggested that CO is unlikely to be directly reducing FEV_1, instead acting as a surrogate for other air pollutants that were not measured, such as PM. Furthermore, these results may be confounded by increased pollutant exposure due to greater time spent outside or exercising, because of the improved asthma control imparted with maintenance medication use. While harmful effects cannot be ruled out, the fact that similar results were seen with two very different classes of maintenance medication is consistent with confounding.

Apparently harmful effects of ICS use on FEV_1 were also demonstrated in an earlier study conducted in Detroit (Lewis et al., 2005) (Table 1). This study identified an association between increased PM_{10} or O_3 exposure and reductions in FEV_1, only amongst those children who were taking a maintenance ICS, in a cohort of children with approximately 50% having mild, and 50% moderate to severe, asthma. The authors of this study suggested that rather than increasing harm, taking an ICS was a marker of increased asthma severity and susceptibility to air pollution. Nevertheless, in a later study conducted by the same group, those volunteers taking an ICS again appeared to have worse asthma symptoms following air pollutant exposure than those not taking medications (Lewis et al., 2013). This study followed a cohort of 298 asthmatic children from lower-income families living in the southwest and east side of the city for two weeks each season, over 11 seasons between 1999 - 2002. Symptom diaries completed during the study weeks were evaluated with respect to air pollution measurements ($PM_{2.5/10}$, O_3) at two community-level monitors. In this cohort, only 9.7% of children used ICS, 13.7% used non-steroid maintenance medications, 43.3% used short-acting $beta_2$-adrenoceptor agonists (SABAs) and 33.9% had no medication use. Significant correlations were identified between 1-hour peak concentrations of O_3 over 3-5 days and asthma symptoms (Lewis et al., 2013). Significantly increased risk of symptoms, including wheeze and shortness of breath, following increased O_3 exposure were only found in those on ICS in odds ratio models. The association of $PM_{2.5}$ concentrations with asthma symptoms also reached significance in those children taking ICS. Greater effects of air pollution on health were seen in residents of southwest Detroit, than in those from the east side, despite a lower percentage of children from southwest Detroit using ICS. The authors again contend that the increased vulnerability of children taking ICS was because, in this population with low overall use, taking a corticosteroid was a marker of more severe asthma.

Two studies performed by different research groups in the US separately identified an association between increased air pollution

exposure and exhaled NO, in asthmatic adults and children respectively (Delfino et al., 2006; Qian et al., 2009). In the first of these Delfino *et al.* recruited 45 children with moderate asthma in southern California and had them wear a personal air pollution monitor during waking hours, complete diaries including information on maintenance medication use and collect exhaled breath in non-reactive mylar bags over 10 days (Delfino et al., 2006). This study indicated a significant positive association between $PM_{2.5}$ exposures and FeNO, a marker of lung inflammation, only in those children taking ICS. The second study enrolled children from a clinical trial known as the Salmeterol Off Corticosteroids Study running in 6 major US cities (Qian et al., 2009). This study enrolled volunteers and took place in 1997-1999, before LABA monotherapy in asthma was banned (Cazzola & Matera, 2007; Sears, 2009). During a run-in period of 6 weeks, volunteers took an ICS twice daily, before being randomized to receive either an ICS, LABA or placebo twice daily over 4 months (Qian et al., 2009). During scheduled research visits in the randomized portion of the study volunteers exhaled into mylar bags from which eNO was later quantified. Exhaled NO results were then associated with data collected in the four proceeding days from nearby US environmental protection agency air pollution monitors. These data indicated a correlation between higher NO_2 readings and increased eNO in children randomized to receive either ICS or LABA (Qian et al., 2009). Associations were also identified between increased PM_{10} levels and eNO in those volunteers on LABA, but a significant correlation was not identified in the children on ICS or placebo. These results suggest a correlation between high levels of air pollution and lung inflammation, which is not reduced or prevented even in those taking ICS. This may indicate confounding with other factors, such as increased time spent outdoors, a degree of air pollution-induced glucocorticoid resistance or an apparently inflammatory action of ICS treatment.

Increased susceptibility to the effects of air pollution could also be due to the enhanced bronchodilation provided by SABAs or maintenance medications, including ICS, through bronchodilation and reductions in mucus respectively, which could open up the lungs allowing greater exposure. This could enhance the PM load penetrating deep into the lungs that may subsequently mediate additional symptoms following, for example, greater use during winter (Lewis et al., 2005; Qian et al., 2009). Another explanation is that use of long-acting β_2-adrenoceptor agonists (LABAs) has been associated with increased inflammation when taken without an ICS, in asthmatics following exposure to air pollution relative to those taking a placebo (Qian et al., 2009). Enhanced inflammation may reflect the increased expression of cytokines, and other mediators, that can be induced by LABA monotherapy (Cazzola & Matera, 2007; Holden et al., 2010; Yan et al., 2018). Seasonal variation may also be confounded by peaks of respiratory infections, though most epidemiological studies try to control for this (Eggo, Scott, Galvani, & Meyers, 2016; Goodman, Loftus, Liu, & Zu, 2017; Jartti & Gern, 2017). In the context of COPD, there is evidence that taking an ICS increases the risk of pneumonia (Kew & Seniukovich, 2014). Therefore, despite the apparent protective effects of ICS on spirometry and asthma symptoms in some studies, harmful effects cannot be ruled out.

5. Controlled human exposure studies

The gold standard to evaluate the effects of air pollutants on humans are controlled exposure studies, which use a facility or different locations to deliver control and specified exposures, usually in randomized order and with washout periods between visits (Ghio, Sobus, Pleil, & Madden, 2012). Typically, features of the exposure can be controlled, including temperature, relative humidity, exposure length and concentrations of specific pollutants. By performing multiple exposures with each volunteer, often with filtered air exposure as a control, each individual can act as their own control (reducing or eliminating confounding factors, such as individual genetic variations). However, such studies are typically limited to acute, short-term (hours-days) time scales, largely exclude those with more advanced disease, for example with moderate to severe asthma or COPD, and usually only enroll a modest number of volunteers (Ghio et al., 2012). Furthermore, the acute timeframes of such studies may hamper analysis of the effects of air pollution exposures on glucocorticoid resistance, given that most diagnosis guidelines suggest evaluation over two weeks with a higher-dose oral corticosteroid.

To the best of our knowledge, no randomized crossover study has been published with the same volunteers exposed to air pollution, in the presence and absence of an ICS. The relevant experimental studies that have been performed in humans include volunteers uniformly taking ICS during controlled exposures or compare endpoints in volunteers on ICS to those not taking ICS. In either case, it is difficult to accurately determine the effects of air pollution exposure on ICS treatment, as observations in this context are easily confounded by differences (other than ICS treatment status) between individuals. Nevertheless, Nordenhäll *et al.* conducted a controlled human exposure study in Sweden with fourteen adult asthmatics who were taking the ICS budesonide at doses of 400-1200 μg over 24 h (Nordenhall et al., 2001). These volunteers were exposed to either filtered air or diesel exhaust standardized to 300 $\mu g/m^3$ of PM_{10} for one hour on separate visits in winter. DE significantly increased airway hyperresponsiveness, by 0.97 doubling concentrations as measured by methacholine PC_{20}, airway resistance and sputum interleukin 6 (IL6) levels, despite ICS use. Likewise, a study conducted in London showed that walking for 2 h along Oxford street (higher air pollution; median 28.3 $\mu g/m^3$ of $PM_{2.5}$) relative to walking in Hyde Park (lower air pollution; median 11.9 $\mu g/m^3$), lead to significantly larger reductions in FEV_1 and FVC (McCreanor et al., 2007). Additionally, despite 39% of the mild asthmatics relative to 86% of the moderate asthmatics taking ICS during the study, greater effects of air pollution were seen in the moderate asthmatics. These results suggest that air pollution is more harmful in severe asthma and potentially that the harmful effects of DE exposure may not be blocked by ICS, though differences between those receiving and not receiving medication were not detailed in the paper.

Larsson *et al.* conducted a similar study in Stockholm, Sweden in which 14 mild asthmatics were exposed for 2 h to either the polluted air in a tunnel, through which 120,000 vehicles a day passed (80 $\mu g/m^3$ of $PM_{2.5}$), or to the clean air of a hospital laboratory (Larsson et al., 2010). In this study six of the volunteers were on ICS/LABA combination medication, while one was on ICS alone and the authors separated out findings on this basis. In those not on ICS, PEF values were significantly decreased relative to control both during and after road tunnel exposure. Conversely, no significant effects were seen in those taking ICS, though this may merely be due to greater variability in this cohort, as a trend towards significance was seen for PEF. Levels of IL10, IL12 and TNFα were also increased in those not on ICS, but data on effects in the ICS group were not reported.

A more recent controlled human exposure study compared the effects of 2 h of DE (100 $\mu g/m^3$ PM_{10}) exposure in mild asthmatics (β_2-adrenoceptor agonists on demand), moderate asthmatics (on ICS) and healthy controls (Behndig et al., 2011). Significant increases in bronchial wash neutrophil counts, myeloperoxidase, and IL6, were seen in healthy controls following DE exposure, but no significant effects were seen in the mild or moderate asthmatics. Nonetheless, FEV_1 significantly decreased after DE exposure, relative to filtered air in the asthmatics and PEF showed a trend towards a decrease, but this did not reach significance. The authors suggest that there was considerable variability in lung function amongst the asthmatics, with some displaying clinically relevant drops. Nevertheless, this study suggested that asthmatics may have reduced induction of airways inflammation relative to healthy controls following DE exposure. However, whether this difference was mediated in part by the medications these asthmatics were taking, or was due to other confounding factors, remains unclear.

Data from the studies described above suggests, but does not prove, that exposure to air pollution may reduce the effectiveness of the ICS used. Because these studies do not include direct comparisons of the effects of air pollution exposure alone (in the same individuals, each in the presence and absence of an ICS) direct effects on corticosteroid resistance cannot be determined. For example, the ICS may be normally effective, but simply unable to reduce all effects of the air pollution exposures. The lack of direct evidence of air pollution inducing glucocorticoid resistance from controlled human exposure studies remains a substantial gap in our knowledge of this area.

6. Mechanisms and molecular evidence for air pollution-induced glucocorticoid resistance

A number of cellular mechanisms have been shown to contribute to the development of glucocorticoid resistance in *in vitro* models, including increased cytokine expression, alterations in post-translational modifications, decreased ligand or DNA binding by GR, impaired translocation, increased expression of the GRβ isoform, increased activation of MAPK, NF-κB and AP-1 pathways, and changes in histone acetylation/deacetylation (Fig. 1) (Trevor & Deshane, 2014). While the mechanisms by which cigarette smoke, a model air pollutant also comprised of gasses and PM, induces glucocorticoid resistance still need to be fully clarified, a number of effects have been proposed to contribute. Cigarette smoke induces oxidative stress in the lungs, with enhanced levels of hydrogen peroxide (H_2O_2) detected in exhaled breath condensate, increases neutrophilia and enhances release of proinflammatory cytokines, such as CXCL8, IL4 and TNFα which may contribute to the development of resistance (Byron, Varigos, & Wootton, 1994; Chalmers et al., 2001; Horvath et al., 2004; Ito et al., 2001). Smoking may also enhance the risk of acquiring and the severity of respiratory infections, thereby increasing the risk of developing exacerbations, possibly through decreasing interferon (IFN) β and enhancing CXCL8 expression (Eddleston, Lee, Doerner, Herschbach, & Zuraw, 2010; Venarske et al., 2006). As with cigarette smoking, the majority of studies have identified activation of oxidative stress pathways as the primary mechanism through which the effects of air pollution are mediated (Xiao, Wang, Li, Loo, & Nel, 2003).

6.1. Oxidative stress

Oxidative stress results from an imbalance between the normal or induced production of reactive species, including superoxide anions, peroxynitrite, H_2O_2, or hydroxyl, alkoxy or peroxy radicals, and the effectiveness of antioxidant defences, including the cellular antioxidants glutathione, superoxide dismutase and catalase (Lodovici & Bigagli, 2011). Oxidative stress can cause the oxidation of proteins and lipids, including GR, often altering their function and can induce both DNA lesions (as shown by increased 8-oxo-dG excretion) and the formation of DNA adducts, potentially changing gene expression (Kelly & Fussell,

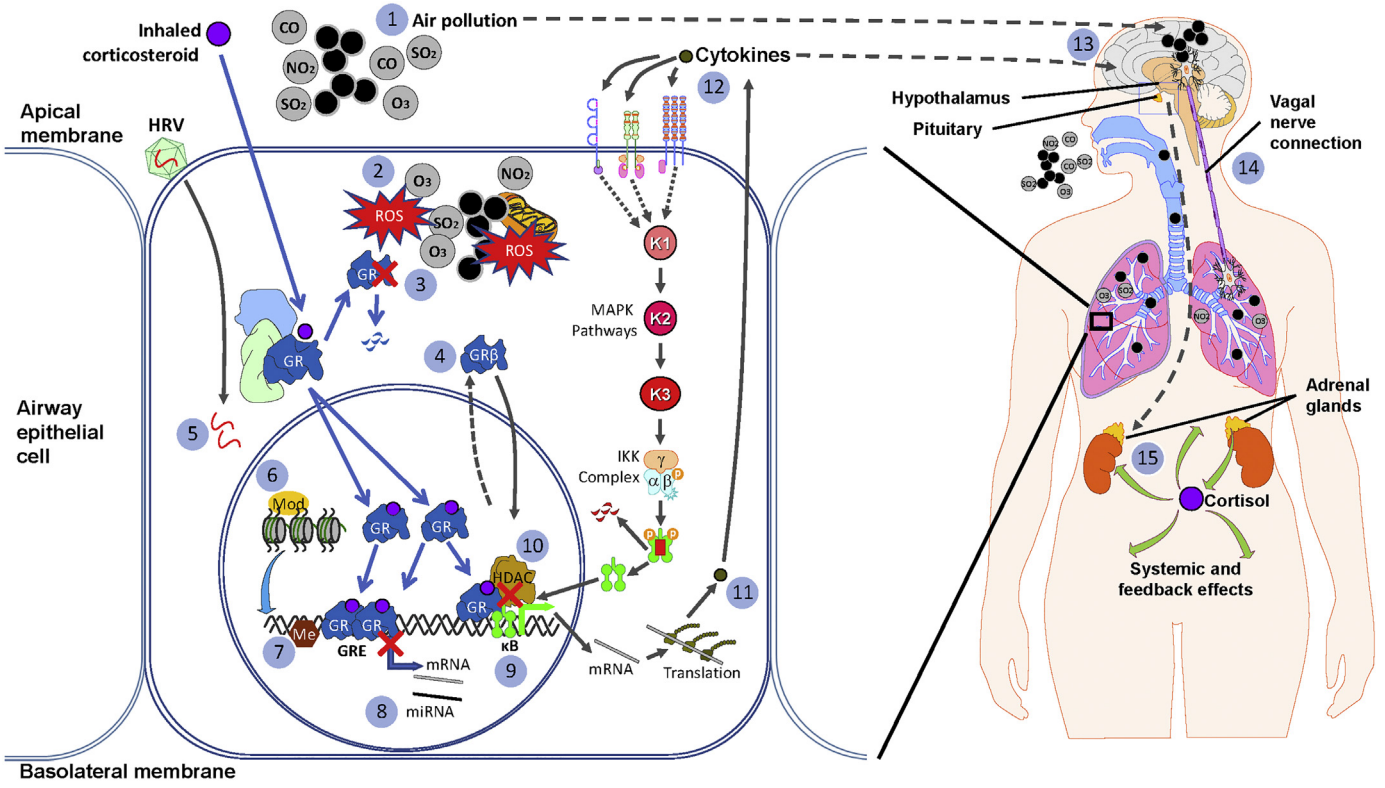

Fig. 1. Mechanisms through which air pollution could reduce the effectiveness of inhaled corticosteroid. 1) Air pollution comprised of particulate matter and gases is breathed into the lung. 2) Gases and particulate may activate, or enter, airway epithelial cells contributing to, or causing generation of, reactive oxygen species (ROS), for example through interactions with mitochondria. 3) ROS or air pollution components such as O_3 can directly oxidize GR, modulating glucocorticoid-inducible activity. 4) Air pollution may also mediate increased expression of GRβ, which may act as a dominant repressor of GR activity. 5) Air pollution exposure may enhance the severity and frequency of viral respiratory infections, such as with human rhinovirus (HRV), which can induce glucocorticoid resistance. 6) Air pollution or air pollution-induced ROS may alter histone modifications (Mod), 7) DNA methylation or 8) microRNA expression, reducing transcription or translation of glucocorticoid-inducible anti-inflammatory genes. 9) Increased NF-κB expression, or activation, may reduce GR activity either by directly binding or through competition for transcriptional cofactors and machinery. 10) As with cigarette smoke exposure, air pollution may decrease the expression or activity of histone deacetylases (HDACs) reducing repression of NF-κB-mediated inflammatory transcription. 11) Air pollution exposure may enhance NF-κB activity and the production of inflammatory cytokines, such as tumor necrosis factor α (TNFα) and IL6. 12) Cytokines released from air pollution exposed epithelial cells may act in an autocrine or paracrine manner on airway epithelial cells, mediating activation of mitogen-activated protein kinase (MAPK) and NF-κB signalling pathways. 13) Air pollution exposure may mediate activation of the hypothalamic pituitary adrenal (HPA) axis. This may result from fine particulate matter and/or cytokines reaching the brain via the circulatory system. 14) Activation of the vagus (or trigeminal) nerves may transmit signals to the brain that may also stimulate the HPA axis. 15) HPA axis activation induces cortisol release from the adrenal glands, which may then act as an antagonist in cells also exposed to ICS reducing HPA axis activation and mediating systemic effects.

2015). Reactive oxygen species (ROS) are important in defence against pathogens and are routinely generated in cells, by, for example, mitochondria, as 2-5% of electrons leak during transfer between electron transport chain complexes (Morgan, Kim, & Liu, 2008). Superoxide anions can also be generated by the reduction of oxygen by transferring electrons from nicotinamide adenine dinucleotide phosphate (NADPH) in NADPH oxidase complexes. Other enzymes, including cyclooxygenases, lipoxygenases, xanthine oxidase, myeloperoxidases and cytochrome P450 enzymes, can also generate ROS.

Ozone is a potent ROS that can directly oxidize many proteins and lipids, potentially including GR. However, other forms of air pollution, including PM, are also known to enhance the production of ROS in the lung epithelium (Fig. 1). For example, exposure to DE may modulate cytochrome p450 reductase activity or damage mitochondrial membranes, leading to superoxide production or release (Xiao et al., 2003). Additionally, ROS may be generated on the surface of particles containing metals, such as iron, cadmium, and chromium, capable of catalyzing the production of hydroxyl radicals (Lodovici & Bigagli, 2011). This may in part explain why smaller particulate fractions enhance asthma symptoms, as, in addition to their ability to penetrate deeper into the lungs, they have a much greater surface area to catalyze the generation of ROS (Peters, Wichmann, Tuch, Heinrich, & Heyder, 1997). Our data indicate that DE-induced airway hyperresponsiveness is reduced in volunteers taking the antioxidant N-acetylcysteine (NAC), suggesting an important role for oxidative stress in modulating lung function (Carlsten, MacNutt, Zhang, Sava, & Pui, 2014; Tashakkor, Chow, & Carlsten, 2011). Furthermore, oxidative stress and inflammation are affected by allele variants (polymorphisms) in oxidative stress response genes, including members of the glutathione S-transferase (GST) gene family, and these may modulate airway hyperresponsiveness after air pollution exposure (Carlsten et al., 2016; MacIntyre et al., 2014; Zhang et al., 2014).

An air pollution-mediated increase in ROS may directly reduce glucocorticoid responsiveness, as GR is often considered a redox-dependent transcription factor (Van Bogaert, De Bosscher, & Libert, 2010). H_2O_2 is a potent reactive oxygen species and has been used extensively to model oxidative stress in *in vitro* experiments (Sies, 2017). A number of experiments have also shown that H_2O_2 can mediate glucocorticoid hypo-responsiveness or even resistance (Rider et al., 2011; Rossios et al., 2012). For example, Rossios *et al.* showed that H_2O_2 exposure reduced corticosteroid sensitivity in U937 cells (Rossios et al., 2012). Both H_2O_2 and cigarette smoke extract (CSE) exposure increased phosphorylation of serine 437 of protein kinase B/Akt and decreased HDAC activity in U937 cells, which could contribute to the development of resistance (Marwick, Ito, Adcock, & Kirkham, 2007; Mercado et al., 2011; Rossios et al., 2012). Furthermore, both H_2O_2 and CSE exposure have been shown to curtail the reduction in lipopolysaccharide-induced CXCL8 and TNFα secretion mediated by a glucocorticoid (Milara et al., 2011). We have also previously shown that H_2O_2 concentration-dependently reduces glucocorticoid-induced activation of a reporter system modelling glucocorticoid-inducible gene expression in human lung epithelial BEAS-2B cells (Rider et al., 2011).

Data from asthmatics also supports the association of oxidative stress with ICS responsiveness (Obaidi & Samarai, 2008). Modulation of responsiveness may occur with exposure to H_2O_2 decreasing, and enhanced expression of thioredoxin reductase 1 increasing, GR activity (Sohn et al., 2007; Wang et al., 2000). Glucocorticoid activity can also be decreased or enhanced by knockdown or overexpression of thioredoxin respectively (Makino et al., 1996). Furthermore, oxidative stress may reduce the feedback of glucocorticoids on the HPA axis, as treatment of corticotroph cells with H_2O_2 decreased the suppression of proopiomelanocortin (POMC; the precursor gene to ACTH) promoter activity and GR translocation (Asaba et al., 2004). This sensitivity to ROS appears to be mediated through the oxidation of GR, principally at the C481 residue within the nuclear localization 1 signal, leading to impaired nuclear translocation (Okamoto et al., 1999). A number of metals, including cadmium, chromium, and lead that can be found in air pollution PM may also affect glucocorticoid activity (Marketon & Sternberg, 2010).

Nitric oxide (NO) is an air pollutant that can also be generated endogenously by three nitric oxide synthase (NOS) enzymes, NOS1, 2 and 3 (previously called neuronal, inducible and endothelial NOS, respectively) through an NADPH dependent reaction (Yates, Kharitonov, Robbins, Thomas, & Barnes, 1995). NO is increased in the exhaled breath of asthmatics relative to healthy controls and as such is considered a marker of airway inflammation. NO may directly affect glucocorticoid activity by reacting with cysteine residues to form S-nitrosothiols in the GR DNA and ligand binding domains (Van Bogaert et al., 2010). However, whether this results in increased or decreased activity is variable, depending on factors including the cell type and the NO concentration.

6.2. Cytokines and activation of proinflammatory signalling pathways

Oxidative stress can cause the activation of inflammatory signalling pathways in lung epithelial cells and alveolar macrophages, including the p38, extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) MAPKs. For example, some effects of O_3 occur through the activation of p38 MAPK, as the inhibitor SB239063 decreases airway neutrophilia and IL17 expression in exposed mice (Bao et al., 2014). Glucocorticoid-inducible DUSP1 expression was also attenuated following O_3 exposure. The use of the p38 MAPK inhibitor SB239063 partially reversed the repression of glucocorticoid activity and modestly enhanced DUSP1 expression (Bao et al., 2014). JNK MAPK activation may also be enhanced and prolonged by ROS, potentially through activation of the MAP3K ASK1 and inactivation of dual specificity phosphatases (Van Bogaert et al., 2010). MAPK pathway stimulation following air pollution exposure may mediate the downstream activation of the transcription factors NF-κB and AP-1 (Kelly & Fussell, 2015). For example, exposure to air pollution in a road tunnel significantly increased expression of AP-1 component c-Jun in the nuclei of bronchial epithelial cells from healthy volunteers (Larsson et al., 2007). The transcription factors AP-1 and NF-κB can enhance the production of numerous inflammatory cytokines and chemokines, including TNFα, IL2, 6, 8, 13 and 17.

Cytokines induced by air pollution may also contribute to reduced glucocorticoid responsiveness. In support of a role therein for IL1, the endogenous antagonist IL1RN/IL1RA reduces inflammation and structural damage following exposure to O_3 (Park et al., 2004). As IL1B represses glucocorticoid-inducible gene expression *in vitro*, this may contribute to induced glucocorticoid hypo-responsiveness (Rider et al., 2011). Intranasal DEP and ragweed allergen challenge significantly enhanced the expression of other cytokines, including IL2 and IL4, in human nasal lavages (Diaz-Sanchez, Tsien, Fleming, & Saxon, 1997). These cytokines have been shown to impair the phosphorylation and function of the GR, contributing to glucocorticoid resistance (Pazdrak et al., 2016). Likewise, transforming growth factor β, which has been shown to mediate glucocorticoid resistance *in vitro* (Keenan et al., 2014), can be induced by air pollution exposure (Dai, Xie, Vincent, & Churg, 2003; Tung et al., 2001).

6.3. Effects of TNF alpha

The expression and release of the cytokine TNFα, which can activate NF-κB, is enhanced by exposure to various types of air pollution and may play a role in ICS resistance (Fakhrzadeh, Laskin, & Laskin, 2004; Kumar et al., 2017; Rider et al., 2011). TNFα has been shown to be induced in mice following O_3 exposure, through an NF-κB p50 dependent mechanism (Fakhrzadeh et al., 2004). In C57BL/6J mice, exposure to 100 μg of DEP-induced a significant increase in TNFα levels in BAL, from undetectable to a concentration of 15 pg/ml (Kumar et al., 2017). The soluble forms of the TNF receptors TNFR1 and TNFR2 were also significantly enhanced in BAL. Additionally, TNFα appears to have a

significant role in DEP-induced lung inflammation, with counts of neutrophils, monocytes, dendritic and T cells in BAL 48 hours after exposure significantly decreased in TNFα knock out mice (Kumar et al., 2017). TNFα knock out mice also had significantly lower concentrations of the cytokines CXCL1, CCL2 and CCL20 after DEP exposure, relative to wild-type. Human airway epithelial cells also produce and release TNFα following exposure to PM (Carter, Ghio, Samet, & Devlin, 1997) and a trend towards increased expression in BAL was seen following exposure to either DE or allergen in one of our human crossover studies (Carlsten et al., 2016). In another controlled human exposure study, increased levels of TNFα were found in nasal lavage from mild asthmatics with direct exposure to ambient air pollution in a road tunnel, as compared to clean air (Larsson et al., 2010).

TNFα has been shown to decrease corticosteroid responsiveness (and vice versa) in numerous studies (Van Bogaert et al., 2010). For example, TNFα significantly reduced the glucocorticoid-induced activation of a simple GRE reporter and expression of the gene CDKN1C (Rider et al., 2011). Mechanistically, TNFα mediates NF-κB and AP-1 activation and these transcription factors may subsequently bind to and impair GR activity (Van Bogaert et al., 2010). Likewise, TNFα- and IFNγ decreased GR transrepression of cluster of differentiation (CD) 38, via induction of GRβ or interferon regulatory factor 1 (Tliba et al., 2008; Tliba, Cidlowski, & Amrani, 2006). Alternatively, reduced GR activity may occur through competition for shared cofactors (squelching), including the p160 family members nuclear receptor coactivator (NCOA) 1/SRC1 and NCOA2/GRIP1 (Van Bogaert et al., 2010).

6.4. Effects of the IL17 cytokine family

Increased IL17 expression is often found in severe asthma and has been associated with glucocorticoid resistance (Brandt & Hershey, 2016). Brandt *et al.* exposed BALB/c mice to 100 μg of DEP, the allergen house dust mite (HDM) or the combination, in the absence or presence of 2 mg/kg of the glucocorticoid dexamethasone and/or 200 μg of an anti-IL17A antibody. DEP exposure significantly increased BAL neutrophil counts and, in the presence of dexamethasone, this count was significantly increased consistent with data showing that glucocorticoids enhance neutrophil survival (Liles, Dale, & Klebanoff, 1995). The combination of DEP and HDM significantly increased counts of eosinophils, Th2 and IL13+/IL17A+ cells in BAL. However, these BAL cell counts were partially, but significantly, decreased by dexamethasone. With the addition of anti-IL17A treatment to DEP+HDM+dexamethasone, a trend was seen towards a greater reduction in eosinophil counts and the increase in neutrophil numbers was modestly reversed, compared to an IgG control antibody. However, in a methacholine challenge with HDM+DEP, airway resistance was modestly decreased by dexamethasone, and the reduction in resistance was significantly enhanced by anti-IL17A treatment. The authors conclude that these responses indicate a degree of glucocorticoid insensitivity is induced by DEP and HDM exposure, and that glucocorticoid effectiveness can be enhanced with anti-IL17A treatment, suggesting a possible role for IL17 in air pollution-induced glucocorticoid resistance (Brandt & Hershey, 2016). Ozone exposure in rats also enhanced IL17A levels in BAL and in the presence of metyrapone, which inhibits cortisol synthesis, levels of IL6, CXCL1 and CCL2, and mRNAs of IL6, TNF and CCL2 were also enhanced (Thomson et al., 2016).

6.5. Phosphorylation of GR and expression of GRβ

Sensitivity to glucocorticoids is highly variable within tissues depending on factors including the concentration of unbound glucocorticoid ligand, number of receptors present, patterns of GR phosphorylation and the ratio of GR isoforms α and β (Newton, Leigh, & Giembycz, 2010). Altered phosphorylation of GRα has been shown to reduce or enhance activity depending on the site (Newton et al., 2010; Van Bogaert et al., 2010). For example, JNK, which can be activated by oxidative stress and TNFα, can phosphorylate S226 in the activation function 1 domain of GR, leading to decreased activity. Increased JNK activation could therefore directly reduce GR activity. GRβ has also been hypothesized to reduce glucocorticoid-responsiveness by acting as a dominant-negative inhibitor of GRα (Fig. 1) (Goleva et al., 2006; Hamid et al., 1999; Lewis-Tuffin, Jewell, Bienstock, Collins, & Cidlowski, 2007; Sousa, Lane, Cidlowski, Staynov, & Lee, 2000; Webster, Oakley, Jewell, & Cidlowski, 2001). In a study by Tliba *et al.*, TNFα-induced expression of CD38 in human airway smooth muscle was reversible with glucocorticoid administration (Tliba et al., 2006). However, CD38 expression induced by TNFα in combination with IFNγ or IFNβ was unaffected by glucocorticoid. The authors propose that this is due to increased expression of GRβ, induced by TNFα. As both TNFα and IFNs can be induced by air pollution exposure, this may represent a potential mechanism leading to reduced glucocorticoid responsiveness. However, very low expression of GRβ is found in many cell types, relative to GRα (Gagliardo et al., 2000; Pujols et al., 2002). For example, no GRβ protein is detectable in A549, BEAS-2B and nasal epithelial cells. Additionally, the dominant negative activity shown using overexpression constructs appears to be cell type specific, making repression of GRα by GRβ unlikely to be widely biologically relevant (Pujols, Mullol, & Picado, 2007).

6.6. Effects of microRNA expression

Exposure to air pollution modulates the expression of a number of microRNAs (miRNAs), including some with the potential to contribute to glucocorticoid resistance (Fig. 1)(Wang, Gou, Jiang, & Ouyang, 2017). Our data has shown that expression of miRNAs, including miR21 and miR-144, is increased following DE exposure (Yamamoto et al., 2013). MiR-144 represses the transcription factor nuclear factor-(erythroid-derived 2)-like 2 (NFE2L2/NRF2), which induces cytoprotective genes, including NAD(P)H quinone oxidoreductase 1 (NQO1) and GST family members (Cheng, Ku, & Siow, 2013; Li et al., 2004; Li & Nel, 2006). MiR-21 is upregulated in asthmatics and contributes to ICS-resistant asthma in mouse models by enhancing activation of the phosphoinositide 3-kinase pathway leading to reduced HDAC2 activity (Kim et al., 2016; Sawant et al., 2015). Our data showed that the antioxidant NAC could reduce DE-induced miR-144 and miR-21 expression, suggesting that TRAP exposure affects epigenetic processes by enhancing oxidative stress (Yamamoto et al., 2013). Indeed, genes in the NF-κB pathway are modulated by DE and expression of downstream targets, including chemokine C-C motif ligand 2 and CXCL8, are enhanced (Carlsten et al., 2016; Rider et al., 2016; Salvi et al., 2000).

There is also data demonstrating that miRNA expression can modulate cortisol production, potentially as part of feedback mechanisms (Clayton, Jones, Kurowska-Stolarska, & Clark, 2018; Robertson et al., 2017; Wang et al., 2017). Global reduction of miRNA expression by knockdown of Dicer, the enzyme that processes miRNA, increased cortisol production in a human adrenocortical cell line, suggesting that cortisol production is under negative regulation by miRNAs (Robertson et al., 2017). An interesting recent review by Clayton *et al.* highlights the many miRNAs targeting genes involved in glucocorticoid synthesis and action (Clayton et al., 2018). However, glucocorticoid treatment also had modest effects on miRNAs in a study investigating the effects of lipopolysaccharide and glucocorticoid on lung inflammation in BALB/c mice (Moschos et al., 2007). No significant change in a panel of 104 miRNAs was induced by glucocorticoid alone at 1 hour. However, three hours after treatment glucocorticoid significantly reduced miR-139 expression, while nine miRNAs had significantly decreased expression at 6 hours. Glucocorticoid pre-treatment also diminished expression of a small number of lipopolysaccharide-induced miRNAs, with the majority of effects seen at 6 hours. However, the authors of this review are not aware of any studies in which the effects of glucocorticoid on air pollution-induced miRNA expression has been tested.

6.7. Effects on DNA methylation

Exposure to air pollution has been shown to significantly modulate DNA methylation (Clifford et al., 2017; Panni et al., 2016). Changes in DNA methylation have the potential to affect glucocorticoid responsiveness through modulation of crucial pathway or response genes, or the induction or repression of factors, such as cytokines, that can induce resistance (Fig. 1). Analysis of a randomized, double-blinded, crossover study with exposures to filtered air and DE performed with 16 asthmatic volunteers indicated that DE changed DNA methylation patterns in the blood (Jiang, Sava, Kobor, & Carlsten, 2014). DNA methylation was analyzed using Illumina 450K chips in PBMCs isolated from blood taken before and at 6 and 30 hours after exposure. Analysis showed that 2827 CpG sites were modulated by DE exposure, relative to filtered air. The modulated sites were enriched for genes in the MAPK and NF-κB pathways, and in general, DE mediated hypomethylation, suggesting a mechanism through which expression of proinflammatory genes, including CXCL8, could be enhanced (Carlsten et al., 2016; Jiang et al., 2014). Methylation of miR-21 was also decreased, consistent with data demonstrating that expression of this miRNA was enhanced by DE exposure (Yamamoto et al., 2013).

Carmona *et al.* undertook an analysis of the effects of air pollution on DNA methylation in 90 male participants enrolled in the United States Department of Veterans Affairs Normative Aging Study (Bell, Rose, & Damon, 1972; Carmona et al., 2014). This analysis showed that out of a total of 84 MAPK associated genes evaluated, 11 genes showed patterns of modulation of DNA methylation that corresponded to the concentrations of black carbon air pollution in the preceding 30 days (Carmona et al., 2014). The DNA methylation patterns of a further 10 genes were correlated with sulfate exposure, out of which 2 were also modulated in relation to black carbon exposures. Surprisingly, DNA methylation patterns of the 11 NF-κB associated genes evaluated showed no association with black carbon exposure (although the RelA gene was hypomethylated in a manner that correlated with black carbon and black carbon plus sulfate in the MAPK model), which the authors suggest might be due to the small sample size evaluated. Ambient particulate matter exposure has also been shown to mediate hypermethylation of the tumor suppressor protein p16/cyclin-dependent kinase inhibitor 2A promoter, via increased ROS production and expression of DNA methyltransferase 1 *in vivo* in mice (Soberanes et al., 2012). Hypermethylation of the p16 gene promoter was reduced *in vitro* by treatment with an antioxidant or an inhibitor of JNK MAPK. However, expression of these MAPK genes was not directly determined, so the effects of methylation remain theoretical. If reduced methylation could mediate increased transcription of MAPK and NF-κB associated genes following air pollution exposure, this could decrease the ability of a glucocorticoid to modulate gene expression, potentially contributing to glucocorticoid resistance.

Liu *et al.* evaluated the effects of DEP, the fungus allergen *A. fumigatus* and combined exposure on DNA methylation in splenic CD4+ cells and IgE production in BALB/c mice (Liu et al., 2008). The analysis was focused on the promoters of the IL4 and IFNγ genes and found that they underwent hypo- and hypermethylation respectively, but downstream gene expression was not measured. Allergen-induced IgE production was enhanced by DEP exposure and this correlated with changes in IgE levels. Should effects on gene and protein expression be shown, these data could provide a mechanism through which DEP exposure could enhance allergen-induced asthma development and skewing of the immune system towards a T helper2 phenotype (Liu et al., 2008). We speculate that increased IL4 expression could, in combination with IL2, contribute to reducing glucocorticoid responses following air pollution exposure (Pazdrak et al., 2016). A crossover study in Italian steel foundry workers comparing the weekend to work days showed that while global methylation was unchanged, the NOS2 promoter underwent significant demethylation following exposure to the work environment, which had higher levels of PM_{10} (Tarantini et al., 2009). NOS2 produces NO which may react with cysteine residues in the GR leading to reduced GR activity (Van Bogaert et al., 2010). This highlights a number of ways in which air pollution-induced modulation of DNA methylation could contribute to glucocorticoid resistance.

6.8. Effects of histone modifications

Changes in the pattern of post-translational modifications on histone tails, including acetylation, methylation, phosphorylation, and ubiquitination, modify interactions with DNA and proteins leading to enhanced activation or repression of transcription of associated genes (Brook, Perry, Adcock, & Durham, 2015; Ho, 2010). Simplistically, histone acetylases (HATs) acetylate histones, loosening chromatin structure and enabling transcription, while histone deacetylases (HDACs) remove acetylation from histone tails, decreasing expression from the associated region. Therefore, the balance of HAT and HDAC activity in particular regions of the genome may affect local gene expression (Brook et al., 2015). PM_{10} exposure has been associated with decreased H3K27me3 and H3K36me3 levels, while other modifications, such as H3K9ac, are associated with black carbon exposure (Ding et al., 2017; Zheng et al., 2017). These modifications may enhance chromatin accessibility and contribute to increased inflammatory gene transcription (Bartke et al., 2010; Podlaha, De, Gonen, & Michor, 2014).

GR is thought to recruit HDACs, including HDAC2 and HDAC3 to pro-inflammatory transcription factor complexes during both negative GRE and tethered transrepression, resulting in deacetylation of histones and contraction of chromatin structures, preventing inflammatory gene expression (Hua, Ganti, & Chambon, 2016; Hua, Paulen, & Chambon, 2016; Ito, Barnes, & Adcock, 2000). Treatment with H_2O_2 or TNFα increases HAT activity (Ito et al., 2002; Rahman, 2002). Enhanced HAT activity and reduced HDAC1 and 2 function were found in biopsies from individuals with asthma, relative to healthy controls, which could contribute to inflammation. Additionally, severe inflammation and cigarette smoke, which can contribute to glucocorticoid resistance development, have been shown to reduce the expression and activity of HDACs (Hew et al., 2006; Ito et al., 2001; Ito et al., 2005). Other air pollutants, such as diesel exhaust, which induce oxidative stress and increased expression of cytokines, including TNFα, could potentially have a similar effect. Indeed, DEP has been shown to mediate increased acetylation of histone H4 and degradation of HDAC1 *in vitro*, leading to increased expression of cyclooxygenase/prostaglandin-endoperoxide synthase 2 (Cao, Bromberg, & Samet, 2007). Air pollution exposure may accordingly contribute to glucocorticoid resistance through decreasing HDAC protein expression, potentially via induction of oxidative stress or TNFα production (Fig. 1) (Osoata et al., 2009).

6.9. Interaction of air pollution with respiratory infections

There is some evidence that air pollution enhances respiratory infection, increases symptom severity during infections and impairs the development of specific immunity following infection (Chauhan & Johnston, 2003). Respiratory infections by pathogens, including human rhinovirus (HRV), are also associated with the induction of glucocorticoid resistance (Papi et al., 2013; Proud, 2011). Mechanistically, air pollution decreases mucociliary activity *in vivo* in humans and *in vitro* enhances cell attachment, entry and the expression of CXCL8 and ICAM1, the HRV major group receptor (Helleday, Huberman, Blomberg, Stjernberg, & Sandstrom, 1995; Jaspers et al., 2005; Spannhake et al., 2002). Air pollution has also recently been shown to decrease the expression of host defence peptides, potentially enhancing susceptibility to infection (Piyadasa, Hemshekhar, Carlsten, & Mookherjee, 2017). In a study of 114 asthmatic children, higher exposure to NO_2 was associated with increased severity of respiratory viral infection-induced asthma exacerbations (Chauhan et al., 2003).

In A549 or BEAS2B cells treated with HRV16 glucocorticoid activity was impaired, with decreased DUSP1 expression, 2×GRE reporter

activation, GR translocation and repression of IL1B-induced CXCL8 (Papi et al., 2013; Rider, Miller-Larsson, Proud, Giembycz, & Newton, 2013). Many of these effects were reversed by inhibition of both JNK MAPK and inhibitor of NF-κB kinase subunit beta (IKK2), a member of the activation complex upstream of NF-κB. However, infection with respiratory syncytial virus (RSV) was not NF-κB dependent, but GR DNA binding and glucocorticoid-dependent induction of TSC22D3, FK506 binding protein 5 (FKBP5) and DUSP1 were significantly reduced (Hinzey et al., 2011). Both neutrophilia and IL17 are associated with glucocorticoid resistance and are enhanced during asthma exacerbations, particularly those associated with respiratory tract infections (Corrigan & Loke, 2007; Strickland et al., 2001; Vazquez-Tello, Halwani, Hamid, & Al-Muhsen, 2013). In experimental HRV infections, those volunteers receiving glucocorticoid prophylaxis experienced fewer symptoms in the first two days of their upper respiratory tract infections, but there was subsequently no difference from placebo controls (Farr et al., 1990). This may reflect the induction of glucocorticoid resistance. These data suggest that susceptibility to respiratory infections can be enhanced by air pollution exposure, which is also associated with increased asthma symptom severity. Respiratory infections are also associated with reduced responsiveness to glucocorticoids and enhanced asthma symptoms. Air pollution could therefore plausibly increase the frequency of respiratory infections, induce glucocorticoid resistance and subsequently mediate exacerbation of asthma.

6.10. Systemic effects and feedback

Exposure to air pollution has been associated with systemic effects beyond the lungs, including increased rates of diabetes, headaches, schizophrenia and heart attacks (Curtis et al., 2006). While describing the data supporting these associations is beyond the scope of this review, we will address potential mechanisms through which systemic effects may be mediated and the role such effects may have in glucocorticoid resistance. Systemic inflammation may result from neural signalling from the airways, 'spillover' of lung inflammation into the systemic circulation or transit of PM into the systemic circulation (Fig. 1)(Block & Calderón-Garcidueñas, 2009). Air pollution is also proposed to induce oxidative stress in the airways leading to stimulation of receptors, including transient receptor potential channels, that can mediate activation of the trigeminal or vagus nerves. These nerves can signal to brain areas, including the nucleus tractus soliatarius and the hypothalamus, triggering activation of the HPA axis and release of CRH from the paraventricular nucleus (Kodavanti, 2016; Sirivelu et al., 2006). Air pollution-enhanced lung inflammation could alternatively increase vascular leakiness enabling inflammatory mediators and cells to enter the circulatory system, mediating systemic inflammation and HPA axis activation (Kelly & Fussell, 2015; Kodavanti, 2016). Additionally, there is evidence that smaller fractions of PM, or the compounds attached to their surfaces, can enter the systemic circulation, either directly or after uptake by phagocytosing cells (Block & Calderón-Garcidueñas, 2009). These compounds or PM could then be transferred to sites including the brain, potentially mediating HPA axis activation (Block & Calderón-Garcidueñas, 2009; Crüts et al., 2008).

With systemic effects of air pollution comes the question of how glucocorticoid resistance (that is not due to GR mutations) is mediated throughout the body and whether activation of the HPA axis contributes. Cortisol and most ICS can trigger feedback mechanisms that reduce the release of CRH and ACTH from the hypothalamus and pituitary glands (Herman et al., 2016). This feedback can suppress cortisol release, which is why rapid withdrawal of high dose corticosteroids can induce musculoskeletal pain, fatigue and sometimes fever (Barnes, 2006; Schäcke, Döcke, & Asadullah, 2002). Corticosteroids can also induce downregulation of GR expression (Dong, Poellinger, Gustafsson, & Okret, 1988; Rider et al., 2018). Exposure to air pollution through inducing cortisol production may, therefore, downregulate both cortisol production and activity. This effect could be compounded in those taking ICS through the negative feedback induced by this class of medications (Bondugulapati & Rees, 2016; Broersen, Pereira, Jørgensen, & Dekkers, 2015). Additional complications may be that GR number and reserve may vary between individuals and in different target or 'side-effect' mediating tissues, affecting whether cortisol, in combination with an ICS that behaves as a full agonist, acts as a partial agonist or even as an antagonist (Newton et al., 2010; Prodanovic et al., 2017). Air pollution may, therefore, mediate glucocorticoid resistance secondary to the induction of cortisol. While this mechanism may have less effect in the lungs where ICS delivery is highest, this feedback could contribute to reduced anti-inflammatory activity or even induce resistance to cortisol and/or the ICS in other tissues, potentially allowing greater systemic harm to be inflicted by air pollution.

7. Approaches to overcoming effects of air pollution-induced glucocorticoid resistance?

A number of approaches to reducing glucocorticoid resistance in asthma and COPD have been proposed that could also apply to air pollution-induced insensitivity (Gross & Barnes, 2016). The initial response to inadequate symptom management in asthma is to increase the dosage of the ICS used and see whether this enables control. However, at a sufficiently high dose of ICS, the risk of developing side effects becomes a concern. At, or before, this point the Global Initiative for Asthma guidelines for adults recommend the addition of a LABA (Global Initiative for Asthma, 2017). LABAs have been shown to synergistically enhance symptom control through enhancing corticosteroid effects (Bateman et al., 2008; Giembycz, Kaur, Leigh, & Newton, 2008; Newton & Giembycz, 2016). *In vitro* LABAs have been shown to 'functionally reverse' induced glucocorticoid hypo-responsiveness, by enhancing the ability of the glucocorticoid to induce gene expression or reporter activation (Rider et al., 2011; Rider et al., 2013; Rider, Shah, Miller-Larsson, Giembycz, & Newton, 2015). Combination therapy also appears to decrease the frequency of exacerbations associated with upper respiratory tract infections (Prazma, Kral, Gul, Yancey, & Stempel, 2010). If adequate symptom control is still not achieved, the ICS/LABA dosage can be increased, and other treatments added, including long-acting muscarinic antagonists or theophylline. There is *in vitro* evidence that theophylline may be effective in reversing glucocorticoid resistance by enhancing HDAC2 expression, through inhibition of phosphoinositide-3-kinase-delta (Barnes, 2009). A small trial assessing the benefits of theophylline prophylaxis before SO_2 exposure showed that treatment significantly reduced the bronchoconstriction induced by this air pollutant (Koenig, Dumler, Rebolledo, Williams, & Pierson, 1992).

A large number of additional therapies are under development or are occasionally used by asthmatics, but the majority of these are limited by side effects or have been minimally effective in a general population in larger clinical trials (Gross & Barnes, 2016; Pepper, Renz, Casale, & Garn, 2017). Improved effectiveness of these therapies may occur with careful tailoring to individual phenotypes, such as the patient's level of eosinophilia, neutrophilia or genetic polymorphisms. Targeting specific features of air pollution responses, in conjunction with data on individual phenotypes, may, therefore, be the optimal approach in those affected. For example, monoclonal antibody-based therapies targeted at IL17 may prove more effective in carefully chosen patients living in an area with high levels of air pollution, though side effects remain a concern (Brandt & Hershey, 2016; Pepper et al., 2017). Although there is some evidence that inhibition of NF-κB and MAPK pathways reverses air pollution-induced repression of glucocorticoid activity *in vitro*, drugs that induce minimal side effects while specifically targeting these pathways *in vivo*, have not been developed (Bao et al., 2014; Gross & Barnes, 2016).

There is modest evidence that diet and specific supplements, including antioxidants and vitamin D, may be beneficial in reducing the impact of air pollution exposure, but these have not been proven in large-scale trials (Laumbach, Meng, & Kipen, 2015; Whyand, Hurst,

Beckles, & Caplin, 2018). The use of antioxidants, such as NAC, may be effective in reducing DE-mediated airway hyperresponsiveness (Carlsten et al., 2014; Tashakkor et al., 2011; Yamamoto et al., 2013). Vitamin D supplementation may also be helpful in combatting the effects of PM exposure on IL17A, improving lung function, enhancing ICS activity and reducing exacerbations (Mann et al., 2017; Sutherland, Goleva, Jackson, Stevens, & Leung, 2010). However, identifying and treating the subset of asthmatics who are most likely to see symptom improvement with a particular therapy is currently limited by an incomplete understanding of the mechanisms underlying glucocorticoid resistance (Berry, Brightling, Pavord, & Wardlaw, 2007; Bradley, 2008; Desai & Brightling, 2010; Heffler, Berry, & Pavord, 2007). Therefore, at least in the short term, the most dramatic benefits are likely to come from increased research, improved regulation and greater prevention of exposures.

8. Policy and practice implications

Improved understanding of the effects of air pollution on glucocorticoid responsiveness could be translated into a number of policies or practices, potentially reducing asthma exacerbation frequency and/or severity. Knowledge of the potentially harmful effects of asthma triggers, such as environmental exposures, can lead to improvements through avoidance (Laumbach et al., 2015; Singh & Hays, 2016). For example, successfully stopping smoking, encouraging family members to also quit and avoiding environments where others are smoking will prevent the harm that first- and second-hand smoke has on respiratory health. The severity of asthma exacerbations induced by air pollution exposure may be reduced by having an asthma action plan and access to appropriate medical care, such that enhanced symptoms can be rapidly managed. Indoor allergen reduction can be achieved through frequent vacuuming, washing of animals twice weekly, or by using bed covers to reduce exposure to dust mites (Singh & Hays, 2016). One approach to reducing exposure to the PM component of indoor air pollution is to use HEPA air filtration, through running an air purifier or whole house filtration system (Sublett, 2011). Often such systems will also reduce the airborne concentrations of allergens from, for example, dust mites, cats, and dogs, reducing symptoms in reactive individuals. Likewise, air conditioning systems that include air filtration are beneficial in reducing PM exposure. However, non-filtering or combined air filters which include 'ionic' systems should be avoided, as these machines can release large amounts of O_3 (Sublett, 2011). Avoiding outdoor air pollutants is more difficult without employing bulky, and often not socially acceptable, gas or N95 face masks or other filtration systems (Laumbach et al., 2015).

Unfortunately, the only workable long-term solutions are likely to be the development of cleaner technologies which are hampered by the intrinsic difficulty of discovery, or policy improvements which are comparatively easy to implement, but subject to considerable political negotiation and industry pushback. Of these, evidence-based policy is the obvious way forward. Changes to policy are often required before sufficient money and time are invested in an area, particularly when research may not lead directly to increased profit, but instead a reduction in emissions. Policy development, such as the 1970 Clean Air Act that established regulations on air emissions from stationary and mobile sources in the United States, is clearly both widely beneficial and massively financially productive, saving many multiples of costs through reduced healthcare expenditure and worker days lost to sickness (US EPA, 2011). Improved public policy to spur emissions control appears to be the only practical solution that will reduce air pollution-induced glucocorticoid resistance and asthma exacerbations at the society level.

9. Summary

Glucocorticoids are the most effective anti-inflammatory medication for the treatment of asthma. Nevertheless, many asthmatics experience exacerbations periodically, with observational evidence suggesting that hospitalizations spike during periods of higher air pollution. An explanation for such increased risk is that air pollution enhances oxidative stress in the lungs, leading to increased inflammation and enhanced severity of asthma symptoms. Additionally, air pollution may reduce responses to glucocorticoids or even induce glucocorticoid resistance, leading to a reduction in control of inflammation. There is substantial evidence indicating that cigarette smoke reduces sensitivity to ICS and thus COPD, which is often smoking related, is generally glucocorticoid-resistant. Given the similarity between cigarette smoke and other types of air pollution, it is reasonable to hypothesize that other combustion-derived air pollution may also induce resistance.

Evidence from epidemiological studies generally support an association between higher air pollution exposure and increased use of both bronchodilators, such as SABAs, and maintenance medications, including ICS. Greater air pollution exposure is also associated with increased asthma symptom severity. The association with increased inhaler use may indicate that during periods of heightened air pollution exposure ICS is less efficacious, possibly as a result of resistance. However, this possibility is difficult to disentangle from greater symptom severity induced by air pollution exposure, which itself may require increased medication use. Thus, the number of studies suggesting that ICS use increases susceptibility to air pollution may either reflect confounding (e.g. ICS use as a result of, rather than the cause of, worsened control of airways disease) or that air pollution induces glucocorticoid resistance.

Controlled human exposure studies are the gold standard for experimentally testing the effects of air pollution in volunteers, but we are not aware of any studies that have evaluated the effects of air pollution exposure in the same volunteers in the presence and absence of an ICS. As the controlled human studies to date have compared asthmatics who take an ICS and those who do not, any changes in response to air pollution can be attributed to differences between the volunteers rather than due to the ICS. Accordingly, additionally controlled human exposure studies could fill in gaps left by the uncertainty in the observational literature.

Perhaps the most persuasive evidence for an association between air pollution exposure and glucocorticoid resistance comes from animal and *in vitro* studies. Ozone is a direct oxidant while other components of air pollution, including PM, are known to induce oxidative stress. Oxidative stress has been shown to reduce glucocorticoid-inducible gene expression and repression of inflammatory cytokine production. Mechanistically, increased ROS may directly oxidize GR, induce activation of MAPK or NF-κB pathways that reduce GR signalling, decrease HDAC activity and enhance expression of cytokines that can mediate resistance. Air pollution may also increase the severity and frequency of respiratory infections, which are associated with asthma exacerbations and glucocorticoid resistance. Furthermore, air pollution increases cortisol release which may contribute to systemic symptoms and activate feedback mechanisms that antagonize ICS activity. Changes in DNA methylation, histone modifications or miRNA expression induced by air pollution exposure could also contribute to glucocorticoid resistance. Therefore, further studies, particularly *in vivo*, are encouraged to determine the mechanisms through which air pollution modulates ICS activity.

The adverse effects of air pollution in respiratory diseases may be reduced through improved symptom management using action plans or with the use of specific supplements or targeted therapies. Engineering controls, such as air conditioners or filters, may also be useful in decreasing exposures. However, reductions in ambient air pollution through improved technology and policy remain the most effective way to reduce harm in susceptible populations, including asthmatics. Emission control policies also benefit all members of the local society and may have comprehensive secondary benefits through reductions in contributions to climate change. Whether air pollution induces glucocorticoid resistance remains to be categorically proven, and further studies are therefore warranted.

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Conflict of interest statement

The authors declare no conflicts of interests.

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