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Authors: Reno, Anita L., Brooks, Edward G., and Ameredes, Bill T.

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Mechanisms of Heightened Airway Sensitivity and Responses to Inhaled SO_2 in Asthmatics

Anita L. Reno[1], Edward G. Brooks[2] and Bill T. Ameredes[1]

[1]University of Texas Medical Branch, Texas, USA. [2]University of Texas Health Science Center at San Antonio, Texas, USA.

Supplementary Issue: Ambient Air Quality (A)

ABSTRACT: Sulfur dioxide (SO_2) is a problematic inhalable air pollutant in areas of widespread industrialization, not only in the United States but also in countries undergoing rapid industrialization, such as China, and it can be a potential trigger factor for asthma exacerbations. It is known that asthmatics are sensitive to the effects of SO_2; however, the basis of this enhanced sensitivity remains incompletely understood. A PubMed search was performed over the course of 2014, encompassing the following terms: asthma, airway inflammation, sulfur dioxide, IL-10, mouse studies, and human studies. This search indicated that biomarkers of SO_2 exposure, SO_2 effects on airway epithelial cell function, and animal model data are useful in our understanding of the body's response to SO_2, as are SO_2-associated amplification of allergic inflammation, and potential promotion of neurogenic inflammation due to chemical irritant properties. While definitive answers are still being sought, these areas comprise important foci of consideration regarding asthmatic responses to inhaled SO_2. Furthermore, IL-10 deficiency associated with asthma may be another important factor associated with an inability to resolve inflammation and mitigate oxidative stress resulting from SO_2 inhalation, supporting the idea that asthmatics are predisposed to SO_2 sensitivity, leading to asthma exacerbations and airway dysfunction.

KEYWORDS: sulfur dioxide, asthma, IL-10

SUPPLEMENT: Ambient Air Quality (A)

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CORRESPONDENCE: btamered@utmb.edu

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Introduction

In 2005, it was estimated that 300 million people worldwide suffered from asthma, with a reported mortality rate of 250,000 people annually.[1] Importantly, by 2025, the number of people affected by this disease is expected to grow by more than 100 million, thus reaching approximately 400 million people worldwide.[1] This prediction projects a 25% increase in the global occurrence of asthma over a 20-year period, a rate that exceeds historical rates of occurrence, even as recently as 20 years ago.[1] As high rates of asthma are typically seen in "Western" industrialized nations, the predicted rise is, in part, predicated on the cultural evolution of less developed cultures and nations toward a western style, with increased industrialization, sanitation, and infectious disease prevention. Associated with this industrial development are numerous sources of gaseous air pollutants, such as sulfur dioxide (SO_2), ozone (O_3), and carbon monoxide (CO), which may be associated with increases in asthma prevalence, but are poorly understood with regard to mechanisms of asthma exacerbation.[2–4] Clearly, with the continued industrialization globally, there is some urgency in refining our understanding of the mechanisms behind asthma associated with inhaled environmental exposure to toxicants.

Asthma is a pulmonary disease characterized by airway inflammation (AI) and reversible airway obstruction that leads to increases in airflow resistance and difficulty in breathing. Previously, asthma was viewed primarily as a disease of airway smooth muscle dysfunction and airway hyper-responsiveness (AHR). While still considered a major component, recent thinking, investigation, and therapeutic approaches over the past 20 years have focused on the significant inflammatory component of this disease that modulates airway function. This has led to an emphasis on trafficking leukocytes and cytokine-associated mechanistic pathways of inflammation within the airways and a focus on increases in eosinophil-associated Th-2 cytokines such as interleukin (IL)-4, IL-5, and IL–13.[5–7] Interestingly, asthmatics are also specifically known to be deficient in the production of IL-10,[8,9] a major anti-inflammatory cytokine, within their airways, which may contribute to their inability to resolve airway inflammation; however, the reason behind this deficiency remains unknown.

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Furthermore, recent research has also shown that changes in airway redox conditions through oxidative stress associated with exposure to allergens and environmental toxicants may be a significant factor in the promotion of airway reactivity, and possibly the development and exacerbation of asthma.[10–12] Given that small-molecule gaseous environmental toxicants such as ozone are thought to initiate a local irritative oxidative stress response that can result in direct airway constriction and exacerbation of asthma,[12–14] a similar mechanism may be potentiated by SO_2; however, there has been a decline in research on inhaled SO_2 in recent years. A PubMed search yielded a relatively small number of inhaled SO_2 articles over the past 5–10 years (average 6–19/year).

Thus, there has been a relative decrease in attention received by SO_2 in recent years. Furthermore, there are additional precedents to consider regarding the activity of the airway cytokine network and irritant/oxidative stress mechanisms that may be potentiated with exposure of asthmatics to a gaseous environmental toxicant, such as sulfur dioxide. A PubMed search encompassing the following terms was performed over the course of 2014: asthma, airway inflammation, sulfur dioxide, IL-10, and mouse and human studies. This search indicated that biomarkers of SO_2 exposure, SO_2 effects on airway epithelial cell function, and animal model data are useful in our understanding of the body's response to SO_2, which includes oxidative stress that may be treatable with antioxidant therapy. SO_2-associated amplification of allergic inflammation, as well as promotion of neurogenic inflammation due to chemical irritant properties, may also contribute to those responses.

In this review, we provide information regarding 1) the sources, characteristics, and metabolism of SO_2, 2) biomarkers of SO_2 exposure, 3) effects of SO_2 *in vitro* and *in vivo*, 4) the generation and scavenging of reactive oxygen/nitrogen species (ROS/RNS) following SO_2 exposure, 5) SO_2 as an environmental toxicant that may be important in the exacerbation of asthma, and 6) the importance of oxidative stress and the cytokine network as factors contributing to the responsiveness of asthmatics to SO_2, with special reference to the potential role of IL-10. In all cases presented, we have converted the unitary numbers originally published to values in parts per billion (ppb) for ease of comparisons across studies.

Environmental Sources, Absorption, and Metabolism of SO_2

Sources of gaseous SO_2 in the environment. SO_2 is released as a gas when sulfur-rich fossil fuel is burned (such as coal or diesel), when metal is extracted from ores, and when gasoline is extracted from oil.[15–17] In some industrialized locations, a high probability of SO_2 exposure may be confined to the factory area itself and within the vicinity of several square miles or the original site of its generation.[18,19] Table 1 illustrates average SO_2 concentrations in various cities ("megacities") across the world. Of the cities represented, Harare (Africa), Mexico City (Latin America), and Beijing (Asia) had the highest concentrations of SO_2 (38.2, 26.7, and 24.8 ppb, respectively).[20] Cairo, Mumbai, Sao Paulo, Athens, and the North American cities of Pittsburgh and New York also represent areas in which industrialization has had an impact in increasing exposures to air pollution, most notably SO_2.[20] Coal is often used as a primary energy source, which only exacerbates the problem in those cities in which SO_2 levels are already high.[20] A study conducted in Russia by Nieminen et al. (2013) sought to determine whether living in a heavily industrial (mining) area would be a risk factor for respiratory symptoms.[21] They observed that people living closest to areas of high levels of SO_2 had elevated incidences of sputum production and the presence of chronic cough.[21] This study illustrates the relationship between sulfur dioxide levels and industrialization, and gives insight into the importance of setting air quality guidelines.

Due to the commonplace occurrence of industrial processes mentioned above, exposures to SO_2 can be, likewise,

Table 1. Annual average SO_2 concentrations during 2000–2005 reported from selected cities worldwide (modified).[20]

REGION	CITY (SELECTED)	ANNUAL AVERAGE SO_2 CONCENTRATIONS IN 2000–2005 (approximations; ppb)
Asia	Beijing	24.8
	Hong Kong	6.9
	Tokyo	3.8
	Mumbai	13.4
	All cities (range)	2.3–24.8
Africa	Harare	38.2
	Cairo	15.3
	Johannesburg	6.9
	Cape Town	3.8
	All cities (range)	3.8–38.2
Latin America	Mexico City	26.7
	Bogota	22.9
	Sao Paulo	15.3
	All cities (range)	15.3–26.7
North America	Pittsburgh	13.4
	New York	11.5
	Los Angeles	4.6
	Seattle	3.4
	Vancouver	6.5
	All cities (range)	3.4–13.4
Europe	Athens	11.5
	Berlin	4.6
	Oslo	3.8
	Barcelona	3.8
	All cities (range)	3.1–13.7

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commonplace, which led to adoption of SO_2 exposure standards to protect workers and nearby residents. In 2010, the Environmental Protection Agency (EPA) replaced the existing primary SO_2 standards (annual and 24-hour) with a new 1-hour standard set at a level of 75 ppb (Table 2). The National Institute for Occupational Safety and Health (NIOSH) acceptability standards vary from 5000 ppb (5 ppm) for 15 minutes of SO_2 exposure to 2000 ppb (2 ppm) for 10 hours of exposure (Table 3). Levels of gaseous SO_2 in some polluted urban air are reported as high as 2000 ppb (2 ppm),[18] which can still prove to be problematic for those living with asthma. For example, it is known that the odor detection threshold for humans is approximately 2700 ppb (2.7 ppm), ranging from 330 to 5000 ppb (0.3–5 ppm),[22,23] which means that those suffering from respiratory problems in these industrial areas can live day to day without being aware of their exposure or knowing about the underlying cause of their breathing limitations. Short-term, high-level exposures to SO_2 gas can cause pulmonary edema, while short-term, low-level exposures [as low as 100–500 ppb (0.1–0.5 ppm)] can produce bronchoconstriction in asthmatics.[24–28] However, normal (non-asthmatic) humans exposed to an acute low dose of SO_2 [up to 2000 ppb (2 ppm)] typically do not demonstrate such a response.[29] Most notably, SO_2 has been reported to aggravate airway allergic responses to inhaled allergens,[26,30] signifying that it has properties that can be highly detrimental to atopic asthmatics.

Absorption of SO_2: Interaction of SO_2 with airborne particles. SO_2 is highly water-soluble, forming secondary compounds such as sulfurous (H_2SO_3) and sulfuric (H_2SO_4) acids, a large portion of which, when inhaled, is readily absorbed/converted within the airway.[31] SO_2 can react with other airborne chemical species, forming secondary particulate matter (PM) [eg, ammonium sulfate $(NH_4)_2SO_4$ and gypsum ($CaSO{\cdot}2H_2O$)][32] over a wide range of particle sizes[33]; the fine and ultrafine particles, rich in the acidic ammonium sulfate, are capable of being carried into the distal airways and alveoli.[17,34] For example, in Houston, Texas, the $PM_{2.5}$ (particulate matter with a diameter of 2.5 µm or less) can be up to 40%–50% sulfur oxide-based.[27] Upon impact with the airways, these sulfur oxide-bearing particulates may theoretically dissolve in the airway lining fluid and produce acidic microenvironments, thereby activating "acid" receptors (transient receptor potential; TRP), calcium channels, and acid-sensing ion channels (ASIC), leading to the activation of inflammatory cascades and possibly damaging cell membranes and inducing oxidative stress responses.[34] Thus, sulfur oxides carried on airborne particulates may be an important source of reactive compounds that are not as easily monitored as compared to the gaseous form of SO_2 itself, and may represent an area requiring a significant amount of further study.

Metabolism of SO_2 in the body. Although the respiratory tract is the primary target for SO_2 gas to exert its toxic effects, other organs and systems can also be affected when this gas enters the systemic circulation via the bloodstream.[35] Due to its high water solubility, hydration of SO_2 results in the formation of sulfite (SO_3^{2-}) and bisulfite (HSO_3^-) anions.[35–37] These ions can then be oxidized in the plasma, forming protein S-sulfonates.[35] Gunnison and Palmes (1974) exposed humans to various concentrations of SO_2 [300–6000 ppb (0.3–6 ppm)] for up to 12 hours. They discovered that, as the concentration of SO_2 increased, the level of S-sulfonates also increased.[38] Similar findings have also been described in experimental animal studies.[39] A study conducted by Bechtold et al. (1993) also utilized the presence of S-sulfonate as a potential biomarker of sulfur dioxide exposure. The authors exposed asthmatic subjects to 1000 ppb (1 ppm) SO_2 for 10 minutes and found increased levels of S-sulfonate in the nasal airway lavage fluid (NALF) as compared to air controls.[40] These studies indicate that protein S-sulfonates have the potential to be good indicators of SO_2 exposure. As of yet, no studies have correlated degrees of elevated S-sulfonates with altered respiratory function measurements [eg, forced expiratory volumes after 1 second (FEV_1)], so this needs to be explored.

Studies in sulfite oxidase-deficient animals have proven to be key in deciphering the role that sulfites play in organ toxicity, as well as indicating how cellular defense mechanisms can become overwhelmed. For example, Izgut-Uysal et al. (2005) showed that the phagocytic and chemotactic functions of peritoneal macrophages of normal rats were

Table 2. Evolution of SO_2 primary National Ambient Air Quality Standards (modified).[137]

YEAR	AVERAGING TIME	LEVEL
1971	24-hr	140 ppb
	Annual	30 ppb
1996	(Existing 1971 standards retained)	
2010	1 -hr	75 ppb
	24-hr	(revoked)
	Annual	(revoked)

Notes: Averaging time is defined as the "time period established for specific national ambient air quality standards, which must be used when interpreting air quality data." The 1971 standards were revoked in 2010 because they "would not provide additional public health protection given a 1-hour standard at 75 ppb." The SO_2 regulatory standard is the 99th percentile of 1-hour daily maximum concentrations, averaged over 3 years.

Table 3. Comparison of primary National Ambient Air Quality Standards for SO_2, odor detection, and health effects.

STANDARD	EPA	NIOSH
15 min	–	5000 ppb
1 hr	75 ppb	-
10 hr	–	2000 ppb

Notes: Odor detection threshold: 330–5000 ppb (2700 ppb avg). Health effects: non-asthmatic (>2000 ppb): asthmatic (≥400–500 ppb).

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increased following exposure to sulfite, but were even further enhanced in macrophages from the sulfite oxidase-deficient rats. In 1987, Gunnison et al. observed higher concentrations of sulfite in rats lacking sulfite oxidase compared to those animals competent in the enzyme, which did not bioaccumulate sulfite in their plasma following SO_2 exposure. Given that asthmatics are known to be highly sensitive to SO_2 and, therefore possibly, sulfite, one could speculate that they might have a relative deficiency in the sulfite oxidase detoxification enzyme,[41] but this has yet to be studied. In considering its elimination mechanism from the body, the excretion fate of SO_2 is associated with its cellular metabolism within the mitochondria, as the mitochondrial enzyme sulfite oxidase detoxifies bisulfite, which is typically excreted in the urine as inorganic sulfate.[35,36]

SO_2 Actions in Asthma: (some of) What is Known

Biomarkers of SO_2 exposure. Recent emphasis has been placed on the assessment of biomarkers in the determination of disease, drug, and toxicity effects.[42] Interestingly, some asthmatic patients carry a genetic polymorphism linked to the bronchial hyper-responsiveness that is triggered by exposure to SO_2.[43] For example, the study by Winterton et al. (2001) sought to determine which genetic polymorphism might be responsible for this reaction, and they found that 13 of 62 asthmatic subjects screened had decreased FEV_1 of 12% or greater, as compared to baseline, following inhalation of 500 ppb (0.5 ppm) SO_2 for 10 minutes.[43] This SO_2-induced bronchoconstriction was linked to a polymorphism at position –308 on the tumor necrosis factor (TNF)-α gene promoter [100% (12 of 12) of SO_2 responders versus only 61% (28 of 68) of SO_2 nonresponders], with no additional polymorphisms observed to be involved.[43] At the level of protein production, a protein biomarker study conducted by Liu et al (2009) focused on breath condensate from asthmatic children following SO_2 exposure [3-day average of 5.4 ppb (0.0054 ppm)], in which thiobarbituric acid reactive substances (TBARS) analysis indicated an increase in oxidative stress within their airways. Pulmonary function in those children was reported to decrease after SO_2 exposure, as well,[11] suggesting a significant relationship between SO_2-associated oxidative stress and pulmonary dysfunction. These data suggest that both genetic and protein biomarkers can be used to help monitor and evaluate human exposure to SO_2 (Table 4), which may be of use in future assessments of SO_2 toxicity and, possibly, mechanisms of asthma.

Besides evaluating exhaled breath condensate (EBC) and pulmonary function, other noninvasive techniques have been used to evaluate the extent of SO_2 effects on the lung, following exposure to SO_2.[29] For example, Raulf-Heimsoth et al. (2009) collected NALF samples from healthy non-asthmatic study volunteers exposed to 0–2000 ppb (0–2 ppm) SO_2 for four hours with two moderate exercise intervals. This acute exposure did not induce alterations in exhaled nitric oxide (F_ENO, which can be typically associated with eosinophilic airway inflammation), nor did it induce alterations in biomarkers typically measured within the EBC [leukotriene B_4 (LTB_4), prostaglandin E_2 (PGE_2), 8-isoprostane (8-iso$PGF_{2\alpha}$)] or NALF [Substance P, IL-8, brain-derived neurotrophic factor (BDNF)].[29] Although no significant differences were seen for NO-associated biomarkers tested in the healthy subjects, it is reasonable to postulate that changes in NO-associated biomarkers might be responsible with an increase in airway irritation and inflammation in asthmatic subjects inhaling SO_2, given that exhaled NO has been shown to be elevated in asthmatic patients.[44] While evidence for this potential association remains scant at this time, measures of NO and other EBC components are becoming more routinely available and could provide a wealth of relatively easily obtainable information regarding the effects of SO_2 in both asthmatics and non-asthmatics in future studies of both exposure and therapeutic modulation of its effects.

Biomarkers of systemic inflammation also have been evaluated in plasma collected from SO_2-exposed subjects.[14,45–48] An ambient air pollution exposure study in humans revealed a positive correlation between IL-6 and SO_2.[14] However, fibrinogen and SO_2 were not correlated,[14] even though exposure to high levels of concentrated ambient air particles has been shown to be significantly associated with elevated fibrinogen levels, presumably due to pollutant-associated tissue damage.[46] Two additional studies sought to determine a link between chronic exposure to outdoor air pollutants and the inflammatory biomarkers fibrinogen and C-reactive protein (CRP). Forbes et al. (2009) concluded that concentrations of fibrinogen and CRP were not associated with all four chronic air pollution measurements (PM_{10}, NO_2, SO_2, and O_3); fibrinogen was actually negatively associated. On the other hand, a study conducted by Hoffmann et al., published in the same year (2009), concluded that, at least for men, chronic exposure to particulate matter air pollution was highly correlated with levels of CRP. Similarly, a 3-year study of Japanese children[48] chronically exposed to air pollution [encompassing suspended particulate matter, nitrogen dioxide (NO_2), and SO_2] also reported elevated levels of fibrinogen. This marked variability needs to be further evaluated to assess the effects of gaseous SO_2 on fibrinogen, but suggests that there may be some potentially important association between SO_2 complexed onto particulates, CRP, and fibrinogen, such that CRP and fibrinogen may be measurable biomarkers of SO_2 exposure. These biomarkers would presumably be easily measureable in a simple blood sample, which could be routinely obtained and analyzed with minimal difficulty.

The biomarker studies mentioned above suggest a preliminary and, most importantly, noninvasive way to identify and characterize SO_2-induced lung dysfunction and/or injury, and confirm potential pathways that might be targeted and modified with anti-inflammatory therapy. It is evident that 1) genetics may play an important role in one's susceptibility to the

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Table 4. Pollution-associated biomarkers.

SAMPLE ANALYSIS	STUDY POPULATION	POLLUTANT(S) AND LEVEL OF EXPOSURE	OBSERVATIONS	REFERENCES
Exhaled breath condensate (EBC)	Asthmatic children, ages 9–14	5.4 ppb SO_2, 6.8 ppb NO_2, and 5.4 µg/m3 $PM_{2.5}$; 3-day average during 4-week study	TBARS indicated ↑ in oxidative stress and ↓ in FEV_1	[11]
	Healthy non-asthmatics, ages 19–36	0–2000 ppb SO_2; 4-hr exposure	No change in FeNO, LTB_4, PGE_2, 8-isoPGF$_{2\alpha}$	[29]
Nasal lavage fluid (NALF)	Healthy non-asthmatics, ages 19–36	0–2000 ppb $S0_2$; 4-hr exposure	No change in Substance P, IL-8, BDNF	[29]
Plasma	Non-asthmatic and asthmatic adults, ages 19–48	0–70 ppb SO_2; 2–3-yr study	Positive correlation between SO_2 and IL-6, but not between SO_2 and fibrinogen	[14]
	Non-asthmatics, ages 18–40	8.8–119 ppb concentrated ambient air particles: 2-hr exposure	Air pollution is associated with elevated fibrinogen	[46]
	Non-asthmatics, ages 16–75+	19.5, 17.9, and 16.2 µg/m^3 PM_{10}; 10.2, 13.5, and 8.6 ppb NO_2; 3.6, 2.3, and 1.6 ppb SO_2; 20.4,19.4, 21.4 ppb O_3; medians for years 1994, 1998, and 2003	Fibrinogen and CRP are not associated with air pollutants, fibrinogen negatively associated	[45]
	Non-asthmatics, ages 45–75	37.7 µg/m^3 $PM_{2.5}$; mean for Dec 2000-July 2003	For men, $PM_{2.5}$ exposure is highly correlated with CRP and fibrinogen	[47]
	Non-asthmatic and asthmatic children,and children with wheeze, ages 6–12	26.7–42.7 µg/m^3 suspended particulate matter: 11.7–29.0 ppb NO_2; 4.3–6.3 ppb SO_2; 3- yr study	For children with wheeze, air pollution exposure is correlated with CRP	[48]

Abbreviations: TNF-α, tumor necrosis factor-alpha; FEV_1, forced expiratory volume after 1 second; TBARS, thiobarbituric acid reactive substances; F_ENO, fractional exhaled nitric oxide; LTB_4, leukotriene B_4; PGE_2, prostaglandin E_2; 8-isoPGF$_{2\alpha}$, 8-isoprostane; IL-8, interleukin-8; BDNF, brain-derived neurotrophic factor; IL-6, interleukin-6; CRP, C-reactive protein.

effects of SO_2 in relation to asthma, and 2) this susceptibility may be decipherable using controlled SO_2 exposure studies. Furthermore, as mentioned above, many people, including asthmatics, could be exposed to SO_2 at insensible levels, the results of which, either early or over time, may ultimately be identified with the measurement of biomarkers, such as those discussed above. While further study is needed to more comprehensively assess the relationship of measurable biomarkers with adverse symptoms in asthmatics, the evidence above suggests that biomarkers may ultimately assist in the understanding of the mechanism behind the effects of SO_2 in asthmatics and its possible treatment.

Epithelial cell studies: Effect of SO_2 and derivatives on gene and protein expression. The effects of SO_2 and its derivatives on various asthma-related genes in human bronchial epithelial cells have been studied in order to determine the possible molecular mechanisms of asthma in relation to the fact that airway epithelial cells are the initial cell barrier, or airway contact point, of inhaled SO_2 gas and sulfates on inhaled particulates (Table 5).[49–52] Two studies, published in 2007, utilized the human papilloma virus (HPV)-18 immortalized human bronchial epithelial cell line BEP2D and examined the effects of SO_2 on mRNA and protein expression of epidermal growth factor (EGF), epidermal growth factor receptor (EGFR), intercellular adhesion molecule (ICAM)-1, cyclooxygenase (COX)-2, mucin-5 subtype AC (MUC5AC), and IL-13.[49,50] EGF and its receptor EGFR have been associated with the repair of inflammatory events and production of mucin.[50,53,54] In contrast, ICAM-1 has been found to promote inflammation and hyper-responsiveness in asthma.[50,55] Because COX-2 controls prostaglandin D_2 (PGD_2) synthesis and, additionally, because increased levels of PGD_2 are thought to cause the constriction of airway smooth muscle, it is conceivable that PGD_2-induced narrowing of bronchi and the encouragement of recruitment and endurance of inflammatory cells[50,56,57] could be a mechanism through which SO_2 exerts its effects within the airway. In support of this idea, mRNA and protein levels of EGF, EGFR, ICAM-1, COX-2, MUC5AC, and IL-13 were found to be elevated in BEP2D cells treated with SO_2 derivatives [sodium bisulfite ($NaHSO_3$) and sodium sulfite (Na_2SO_3); 0.0001, 0.001, 0.01, 0.1, and 1 mM], indicating that those asthma-related genes modulate inflammation in the airways and promote hyper-secretion of mucus following SO_2 exposure.[49,50]

Prior to beginning their human epithelial lung cell study, Pelletier et al. (2002) noted that it had not yet been proven that this cell type could be activated by sodium sulfite. The authors subsequently demonstrated such activation by incubating the epithelial cell line A549 with increasing concentrations of sodium sulfite (0.01–10 mM), which resulted in generalized protein tyrosine phosphorylation events and IL-8 production.[51] They also observed adhesion of neutrophils to the sodium sulfite-activated epithelial lung cells following sodium sulfite exposure, which was shown to be independent

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Table 5. Epithelial cell studies with SO_2.

CELL TYPE	OBSERVATIONS	REFERENCES
HPV-18 immortalized human bronchial epithelial cells (BEP2D)	Sodium bisulfite and sodium sulfite-exposed cells (0.0001, 0.001, 0.01, 0.1, and 1 mM; 4-hr exposure) displayed increased transcription and translation of EGF, EGFR, ICAM-1, COX-2, MUC5AC, and IL-13.	[49],[50]
A549	Sodium sulfite-exposed cells (0.01–10 mM; 24-hr exposure) showed initiation of phosphorylation events on the Tyr residue, IL-8 production, and neutrophil adhesion.	[51]
	1. NFκB,ERK1/2, and p38 play an important role in IL-8 gene expression following sodium sulfite exposure (0, 100, 500, 1000, and 2500 μM; 16-hr exposure). 2. Treatment with fluticasone, salmeterol, and montelukast decreased the production of IL-8.	[52]

Abbreviations: EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ICAM-1, intercellular adhesion molecule 1; COX-2, cyclooxygenase-2; MUC5AC, mucin-5 subtype AC; IL-13, interleukin-13; Tyr, tyrosine; NFκB, nuclear factor kappa B; ERK1/2, extracellular signal-regulated kinases 1 and 2.

of intercellular or vascular adhesion molecules ICAM-1/-3, or vascular cell adhesion molecule (VCAM)-1, respectively.[51] Moreover, a study conducted by Yang et al. in 2008 evaluated the effects of various asthma-controlling drugs on sodium sulfite-induced inflammation (0, 100, 500, 1000, 2500 μM) in A549 cells. They found that nuclear factor kappa B (NF-κB), extracellular signal-regulated kinases 1 and 2 (ERK1/2), and p38 all play an integral role in the gene expression of IL-8 after sodium sulfite exposure.[52] Their results further showed a decrease in sodium sulfite-induced IL-8 production following treatment with fluticasone, salmeterol, and montelukast,[52] each of which is known to have differing mechanisms of action (steroid, β-agonist, and leukotriene modifier, respectively). Thus, the studies above strongly indicate that there is significant evidence for the effects of SO_2 on epithelial cell activation.

SO_2 studies in animal models: Guinea pigs. A number of animal studies, notably those of guinea pigs, have investigated the effects of SO_2 on the airways (Table 6).[58,59] Studies in guinea pigs may be particularly instructive and translational in this case because of the relatively enhanced nasal and lower airway sensitivity of that species and its similarity to humans regarding histamine-driven immunoglobulin (Ig)E responses.[60–62] For example, one study in guinea pigs found that inhalation of SO_2 [200,000–300,000 ppb (200–300 ppm) for 4 h/day over 4 days] induced AI and enhanced sensitivity to histamine, which were associated with elevations in ROS.[58] Another study in guinea pigs showed an enhancement in the development of allergen-induced asthma following repeated exposures to low levels of SO_2 [100 ppb (0.1 ppm) for 5 h/day over 5 days].[59] In that study, SO_2-exposed animals had increased enhanced pause (Penh; a measure of airway obstruction, in vivo), increased bronchoalveolar lavage fluid (BALF) eosinophil counts and inflammatory cell infiltration into the lung parenchyma, as well as damage to the bronchiolar epithelium.[59] Here, evidence from guinea pig models has shown that SO_2 inhalation plays a role in exacerbating AI, whereby ROS levels are modulated and associated changes in airway leukocyte infiltrates abound.

SO_2 studies in animal models: Mice. Although mice typically do not have exactly the same sensitivities and driving mechanisms as guinea pigs, they do express aspects of airway inflammation and airway hyper-responsiveness that make them useful models for some comprehensive studies (Table 6).[63–67] For example, inhalation of SO_2 [8400–42,700 ppb (8.4–42.7 ppm)] over a week (6 h/day over 7 days) resulted in lipid peroxidation and a decrease in lung antioxidant levels in mice.[65] A later study by the same group indicated that, as a result of SO_2 inhalation, the sulfite content in the lungs of mice was higher than that in the heart or brain, which might be explained by the fact that the lung is exposed to SO_2 first (as a first-pass organ).[66] An alternative explanation for those data could also be that the enzymatic action of sulfite oxidase is more efficient in the heart, brain, liver, and kidney, as compared to the lung[17,66,68–70]; this will take further study to resolve. Furthermore, measurement of cytokine levels in the lungs of those SO_2-exposed mice also showed a significant skewing of the pro-inflammatory/anti-inflammatory balance toward pro-inflammatory.[67] In contrast to some mice, eg, C57Bl6 and C3 strains that are mild responders,[71] a fairly recent key study in BALB/c mice (typically considered strong AI responders) investigated the effect of acute induction of AI by a combination of inhaled SO_2 [50,000 ppb (50 ppm) for 1 h/day over 3 days] followed by inhalation of ovalbumin, which resulted in a subsequent induction of chronic allergic AI.[63] Importantly, this acute SO_2 exposure model, accompanied by an allergen trigger, exemplified that the exposure to SO_2 promoted a significant enhancement in the AI response.[63] A similar finding was reported in another BALB/c model utilizing a combination of SO_2 inhalation exposure and house dust mite allergen.[64] Thus, evidence from mouse models has shown that allergic AI is highly exacerbated by SO_2 inhalation, and is coupled with changes in ROS levels, pro-inflammatory versus anti-inflammatory balance, and antioxidant responses.

SO_2 studies in animal models: Rats. Lungs and airways of rats have also been studied to elucidate the effects of SO_2 on gene expression related to asthma and apoptosis, as well as xenobiotic-metabolizing cytochrome P450s (Table 6).[72–77] For example, studies by Li et al. measured mRNA and protein levels of MUC5AC, ICAM-1, EGF, EGFR, and COX-2 in

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Table 6. SO_2 experiments in animal models.

ANIMAL MODEL	STRAIN	OBSERVATIONS	REFERENCES
Guinea Pig	Hartley, Dunkin- Hartley	SO_2 (200–300 ppm; 4 hr/day/4 days) inducedAI and enhanced sensitivity to histamine due to elevations in ROS	[58]
		SO_2 inhalation (0,1 ppm; 5 hr/day/5 days) increased Penh, BALF eosinophil counts, and infiltration of inflammatory cells; damaged epithelium	[59]
Mouse	Kungming albino	SO_2 inhalation (8.4, 21.4, and 42.7 ppm; 6 hr/day/7 days) induced lipid peroxidation and decreased anti-oxidant levels	[65]
		Sulfite levels were higher in the lung compared to other organs following SO_2 inhalation (5.3,10.7, and 21.4 ppm; 4 hr/day/7 days) [lower sulfite oxidase levels?]; cytokine levels showed a shift toward pro-inflammatory	[66],[67]
	BALB/c	Exposure to SO_2 (50 ppm; 1 hr/day/days 7, 9, 11) or sodium sulfite (5 mM; days 1–22) promotes an enhancement in the AI response	[63],[64]
Rat	Wistar	OVA compounded with SO_2 (2 ppm; 1 hr/day/days 15–21) enhanced mRNA and protein levels of EGF, EGFR, COX-2, MUC5AC, and ICAM-1 to a greater degree than allergen alone	[73],[74]
		SO_2 exposure (2.7, 5.3, and 10.7 ppm; 6 hr/day/7 days) increased levels of TNF-α, IL-1β, ICAM-1, and iNOS mRNA	[77]
		SO_2 challenge (2 ppm; 1 hr/day/days 15–21) inhibited expression of p53 and bax, while the expression of bcl-2 was promoted	[76]
		SO_2 exposure (5.3, 10.7, and 21.4 ppm; 6 hr/day/7 days) increased bax mRNA levels, while levels of bcl-2 remained unchanged	[72],[77]
		SO_2 inhalation (5.3,10.7, and 21.4 ppm; 6 hr/day/7 days) suppressed the expression of CYP1A1 and CYP1A2	[75]

Abbreviations: Penh, enhanced pause; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase.

allergen (OVA)-exposed, SO_2-exposed, and OVA + SO_2-exposed male Wistar rats. Compared to control rats, OVA alone significantly increased mRNA and protein levels of these asthma-related genes, while OVA co-exposed to SO_2 [2000 ppb (2 ppm) for 1 h/day over 7 days] enhanced the mRNA and protein levels of MUC5AC, ICAM-1, EGF, EGFR, and COX-2 to a greater degree than the allergen inhalation by itself.[73,74] These results further developed and confirmed the *in vitro* data mentioned previously in the epithelial cell studies section. Yun et al. (2011) observed increased levels of TNF-α, IL-1β, ICAM-1, and inducible nitric oxide synthase (iNOS) mRNA in their male Wistar rat model of SO_2 exposure [2700–10,700 ppb (2.7–10.7 ppm) for 6 h/day over 7 days]. Another study using the same strain of rats showed that the expressions of pro-apoptotic genes (p53 and bax) were inhibited by SO_2 challenge [2000 ppb (2 ppm) for 1 h/day over 7 days], while the expression of an anti-apoptotic gene (bcl-2) was promoted.[76] On the other hand, two independent SO_2 exposure studies [encompassing the range 2500–20,000 ppb (2.5–20 ppm) for 6 h/day over 7 days] in male Wistar rats illustrated increases in bax mRNA levels in the lung, while bcl-2 mRNA levels remained the same.[72,77] The reason for the discrepancy in the two studies could be related to the concentration of SO_2 used, or perhaps due to the fine balancing that occurs between pro- and anti-apoptotic genes, in a diseased lung versus a nondiseased lung.[78] Finally, Qin and Meng (2005) observed suppression of cytochrome P450 (CYP)1A1 and CYP1A2 expression in the lungs of rats following SO_2 exposure [5300–21,000 ppb (5.3–21 ppm) for 6 h/day over 7 days], suggesting a potential metabolic or oxidant effect. Taken together, these gene expression data might be indicative of a possible mechanism by which SO_2 encourages and maintains an inflammatory status in the asthmatic lung, while the cytochrome P450 data might indicate a mechanism whereby SO_2 may trigger protective responses within the normal lung.

Generation of ROS/RNS associated with SO_2 exposure. Asthma is an inflammatory disease known to be associated with the generation of ROS as a consequence of ROS-producing leukocytes, most notably eosinophils, neutrophils, and macrophages, recruited to the sites of inflammation and/or injury in the airways.[79] Airway leukocytes also release a wide range of enzymes involved in inflammation. One enzyme implicated in the formation of ROS in the asthmatic lung following SO_2 exposure is nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.[80] Although not necessarily translatable to *in vivo* responses, studies of specific mechanisms within cell culture models can be instructive toward our understanding of the effects of SO_2 in the lung. For example, a study conducted by Beck-Speier et al. (1993) examined the effects of low concentrations of sulfite (0.01–1 mM) on human neutrophils, *in vitro*, and found that NADPH oxidase activity was significantly increased when compared to control cells not exposed to sulfite. Neutrophils are known to have an inherently decreased

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activity of sulfite oxidase, leaving them vulnerable to the effects of sulfite,[68] which may, in turn, be responsible for the elevations in NADPH oxidase activity observed with sulfite exposure. In human alveolar macrophages and peripheral blood mononuclear cells exposed to 300–1500 ppb (0.3–1.5 ppm) SO_2 for 30 or 120 minutes concluded that vast amounts of ROS were produced following activation of these cell types by SO_2.[81] It has also been shown that superoxide production can be triggered by sodium sulfite on its own,[82] and that increases in levels of NADPH oxidase can be circumvented by the addition of superoxide dismutase (SOD), a potent antioxidant.[80] In support of that idea, a study utilizing rat basophilic leukemia cells pretreated with diphenyleneiodinium (DPI; an inhibitor of NADPH oxidase) showed a 50% inhibition of sulfite-induced ROS formation,[83] again demonstrating the strong relationship between sulfite exposure and ROS formation. Thus, cellular NADPH oxidase has been implicated as a crucial enzyme responsible for the oxidative responses upon challenge with sulfite,[83] and may have important ramifications for the effects of SO_2 and particulate-borne sulfites in the asthmatic lung.

Oxidative stress brought on by various cellular insults, or polymorphisms in oxidative stress genes, can promote the generation of free oxygen radicals, most notably superoxide.[84] Superoxide can then complex with and oxidize NO, thus creating the highly reactive species peroxynitrite, which can, in turn, initiate lipid peroxidation in the cell. Empirically, NO protects the cell from the detrimental effects of ROS, but loses this beneficial effect once oxidized by superoxide.[85] Furthermore, activation of NF-κB is regulated by NO, and this activation can be used as a direct indication of NO bioavailability in an oxidant-stress-laden environment.[85] Thus, in the oxidative setting of the asthmatic lung, high levels of NO encourage the development of RNS, which oxidize cellular components, most notably proteins, and create an overwhelming chronic inflammatory status.[86]

ROS/RNS scavenging: A treatment for SO_2 exposure in asthma? Environmental pollutant triggers such as SO_2 are known to promote oxidative stress and AI in asthmatics[11] and in animal models.[87] An important process in the resolution of airway inflammation is the removal of ROS from the cellular environment.[80,85,88–90] Numerous antioxidants, such as glutathione (GSH), heme oxygenase-1 (HO-1), and SOD, have been implicated, and are capable of carrying out this task.[80,90]

Extracellular superoxide dismutase (EC-SOD) is the most abundant SOD in the body, which is highly expressed in mammalian lungs,[88] and may significantly contribute to neutralization of ROS. Ahmed et al. (2011) transfected C10 mouse lung epithelial cells (known to be significant sources of pro-inflammatory cytokines) with human EC-SOD, and observed that NO bioavailability was conserved, which prevented activation of NF-κB, normally a result of oxidative stress. In this case, EC-SOD protected the cells from the detrimental effects of NF-κB activation (via scavenging of superoxide free radical), which is the downstream induction of pro-inflammatory cytokines and mediators. This implies that pulmonary diseases characterized by oxidative stress, such as asthma, compounded with SO_2 inhalation, might be alleviated by the administration of EC-SOD[88,89]; however, this requires further investigation, in the context of SO_2 exposure.

In support of the idea that oxidative status is important in asthma, deficiencies of plasma levels of dietary antioxidants, such as vitamins C (ascorbic acid), E (α-tocopherol), and D, have been associated with lung disease.[91–100] In 1996, Redlich et al. noted the feasibility of using serum and BAL cell levels of vitamin E to predict lung levels of vitamin E. With this knowledge, Trenga et al. (1999) conducted a study that illustrated reductions in plasma vitamin C and E concentrations in asthmatic adults exposed acutely to SO_2 [500 ppb (0.5 ppm for 10 minutes)] and moderate exercise. Those investigators extended the results by supplementing the diets of adult asthmatics exposed to SO_2 with a combined regimen of vitamins C and E, and revealed a marked attenuation of bronchial hyper-responsiveness when compared to those study subjects given a placebo.[99] Likewise, increases in FEV_1 were noted in exercise-induced asthma (EIA) after vitamin C supplementation.[92,96,97] Furthermore, a study by Fogarty et al. (2006) described how a diet supplemented with vitamin C was associated with reduced use of corticosteroids in asthmatics.

Recently, the beneficial effects of vitamin D have also received significant attention.[91,94,100] Over the course of 4 years, the Childhood Asthma Management Program (CAMP) trial sought to determine the relationship, if any, between asthma severity and serum vitamin D levels.[91] This study, and others, have indicated that vitamin D insufficiency is linked to an increased risk for bronchial hyper-responsiveness and lowered lung function (asthma exacerbations), and increased exacerbations requiring emergent care.[91,94,100] However, more recently, Castro and colleagues (2014) have reported that vitamin D supplementation in adults with persistent asthma and vitamin D deficiency did not alter first treatment failure rate or asthma exacerbations.[101] These seemingly divergent findings suggest an age-related difference in the effect of vitamin D supplementation on asthma in the child and adult populations, which needs to be further investigated. Even so, given the implications of dietary antioxidants in lung disease, it is reasonable to consider the use of antioxidants in asthmatics whose asthma may be exacerbated with environmental SO_2 exposure, in which reactive oxidants may play a significant role.

Potential for an SO_2-associated neurogenic inflammatory mechanism. As outlined above, oxidative stress associated with ROS generation may be important in promoting the inflammatory and physiological effects of inhaled SO_2 and inhaled particulate-borne sulfates within the airway. One possible mechanism through which ROS may act to produce exacerbations in asthmatics is through the inherent "irritant" properties of SO_2 and subsequent induction of neurogenic inflammation. Neurogenic inflammation is defined as inflammation stemming from the nervous system following stimulation of chemical irritant receptors on sensory nerves.[102]

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Activation of TRPA1, TRPV1, and ASICs in response to SO_2 and/or secondary acid formation have been associated with the activation of airway inflammation and cough in animal models.[103,104] Neuropeptide mediators such as calcitonin gene related peptide (CGRP), Substance P, and neurokinin A are released from sensory nerves and stimulate effector cells to initiate an inflammatory response.[102,105] Furthermore, neuropeptide release resulting from neurogenic inflammation can mimic the pathology of asthma that is seen in the case of immune-system-induced inflammation[102]; however, these inflammatory responses have been found to be distinct from the typical allergen-induced inflammation regulated by the immune system, suggesting the expression of different asthma phenotypes due to distinct stimuli and mechanistic pathways.[106]

In the presence of a moist environment, such as in the nasal passages and airways, SO_2 converts into sulfuric acid, which can activate chemical irritant receptors and potentially set into motion subsequent non-allergic-associated neurogenic inflammatory responses.[107] Airway acidification is a strong inducer of bronchospasm, and low EBC pH has been associated with acute exacerbations of asthma[108] and poor asthma control.[109,110] The role of chemical irritants, such as SO_2, and their association with neurogenic inflammation have been studied in animal models of asthma.[102,111–113] For example, formaldehyde, a chemical widely present in the environment in household products, cigarette smoke, and industrial exhaust,[114–116] was found to promote a neurogenic inflammatory response that was separate from an allergic immunological response in a mouse model of inflammation.[112] Plasma levels of Substance P were significantly increased in animals exposed to inhaled formaldehyde at the level of 2000 ppb (2 ppm), providing strong evidence for stimulation of pulmonary C-fibers resulting in a non-allergen-associated inflammatory response induced by the nervous system.[112] Similarly, a study of airway injury with low-level inhaled SO_2 [400 ppb (0.4 ppm) for 6 h/day over 3 days] in rats implicated neurogenic inflammation as a "critical pathophysiological mechanism" due to the observations of significantly elevated levels of Substance P in plasma and positive staining for Substance P in C-fibers within the lung tissue.[113] Given that the study by Lin et al. (2009) was the only research article found after searching for the terms "SO_2 and neurogenic inflammation" illustrates the need to possibly shift our thinking toward the potential that the nervous system may play a significant role in the inflammatory response associated with SO_2 inhalation and exacerbations of asthma.

Gaps in SO_2 Knowledge and Research

Potential for an IL-10-deficiency-associated mechanism of SO_2 sensitivity in asthma. The studies and evidence outlined above point to some suggestions as to how SO_2 and particulate-borne sulfates may exert their effects on the airway; however, the question remains as to why asthmatics seem to be highly responsive to SO_2. As shown in Figure 1, it is clear that oxidative stress is an important driver of AI, and that SO_2 promotes ROS production in the lung which can drive AI, possibly through either classical allergen-associated mechanisms or neurogenic mechanisms. While antioxidants may afford some protection from ROS-induced oxidative stress, it is also well established that anti-inflammatory drug treatments, such as corticosteroid administration, substantially reduce AI. This resolution of inflammation, or its suppression in the case of inhaled corticosteroids given as regularly scheduled asthma-controller medication, includes reduced trafficking of leukocytes, particularly eosinophils, as well as reduced pro-inflammatory cytokine and chemokine production.[117–119] These effects may occur, in part, through increases in IL-10 associated with steroid treatment.[117–119] However, the role of IL-10 in the airway response to SO_2 has been essentially unstudied. Considering that the production of IL-10 is deficient in the lungs of people with asthma,[8] there is a potential that this deficiency may be at the core of the apparent hyper-responsiveness of asthmatics to the inflammatory effects of SO_2.

Key animal studies cited above have provided some suggestions regarding the importance of inflammation and its resolution after exposure to SO_2. However, a common limiting characteristic of the prior SO_2 studies is that none has been attempted in a model deficient in IL-10, which presumably would be highly relevant to the case of asthma, as mentioned above. Previously published mouse studies utilizing the IL-10 double-knockout null mutant mouse ($IL\text{-}10^{-/-}$)[120] have identified that a lack of IL-10 results in enhancement of AI,[121,122] which is associated with increased airway iNOS mRNA and iNOS protein,[123] as well as increased IL-4 levels (ie, a predominance of the Th-2 adaptive immune reaction).[124–126] However, none has been performed to determine whether a lack of IL-10 predisposes toward an increased AI and ROS response to SO_2. This shortcoming in our understanding could be important, due to the fact that SO_2 inhalation has been implicated in the production of ROS within the lung, and the fact that asthmatics have increased airway levels of ROS and other inflammatory mediators.[11,63]

Some additional possible hints as to the potential importance of IL-10 in SO_2-exacerbated allergic asthma include that select therapeutic interventions are known to increase endogenous levels of IL-10.[127] Regulatory T cells (Tregs; $CD4^+FoxP3^+$ phenotype), including the inducible type 1 Treg (Tr1), can be utilized for immunotherapy against allergen sensitivity, as reviewed by Ogawa et al.[127] In that case, IL-10 production is upregulated via Tr1 cells, and immune tolerance is subsequently conferred.[128–130] Furthermore, the inducible form of heme oxygenase (HO-1), also known as heat-shock protein 32, is the enzyme that catalyzes the breakdown of heme, and is a probable candidate at the center of this phenomenon. For example, a characteristic of HO-1 is its ability to protect airway cells from ROS damage via anti-inflammatory and anti-oxidative processes involving increased secretion of IL-10 by Tregs and the overall promotion of Treg cell numbers.[90,131–133]

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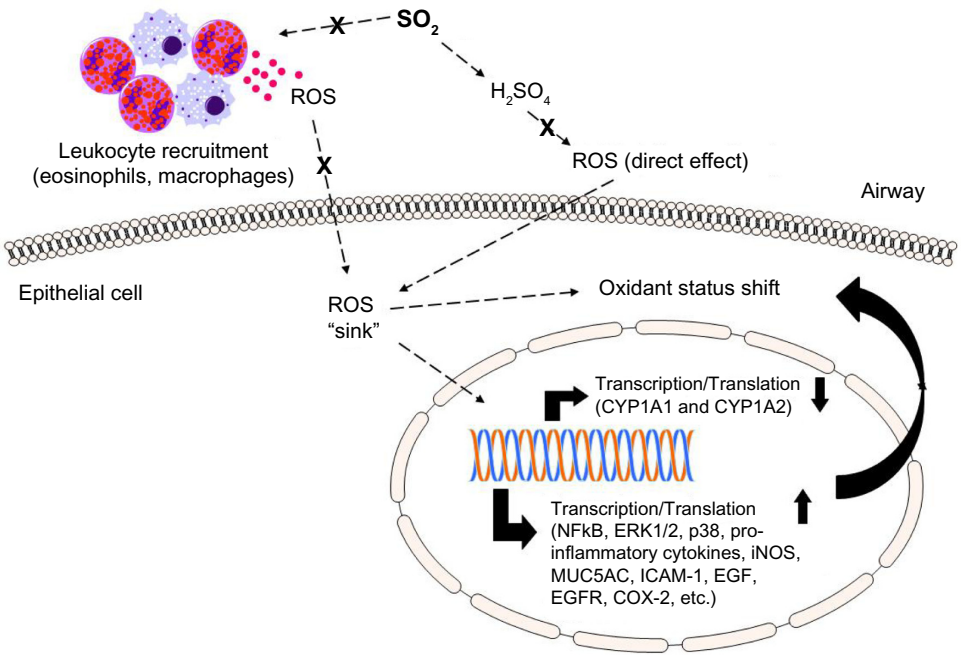


Figure 1. Schematic of SO_2 cellular mechanisms. Effects of leukocyte recruitment in the airway following SO_2 exposure, as well as effects of SO_2 itself, are shown. ROS, as a direct product from SO_2 exposure or via secretion from recruited leukocytes 1) promotes an oxidant status shift within the epithelial cell and 2) modulates gene and protein levels, which feed back into the oxidant status shift within the epithelial cell. X is the site of possible IL-10 inhibitory effects.

Therefore, it would appear essential to retain the functionality of Tregs in the airways. In that regard, specific allergen immunotherapy (SIT), which promotes allergen-specific Treg function, may be a therapeutic possibility to reverse the detrimental effects of SO_2-exacerbated allergic asthma, assuming that further research would support this possibility.

The consequences of IL-10 deficiency in asthma may also play a role in relation to asthmatic susceptibility to environmental toxicant/pollutant triggers, which may act as irritants promoting neurogenic inflammation, as outlined above. This process typically involves an early and late phase immune response, in which pro-inflammatory cytokines are released early (eg, IL-1β, IL-4, IL-5, IL-13, and TNF-α), promoting eosinophilia,[6,134,135] followed by later release of IL-10, which blocks the early-phase-dependent inflammation and decreases eosinophilia.[6,136] Clearly, a deficiency in IL-10, as reported in asthmatics,[8] would likely hamper the resolution of inflammation.

In all, there appears to be suggestive evidence that asthmatics may be sensitive to SO_2, in part due to their inability to make significant amounts of IL-10, and that therapies targeted toward enhancing or restoring this capability might be beneficial. However, our current state of knowledge of this relationship is exceedingly minimal and requires further research.

Conclusion

SO_2 is a recognized environmental toxicant that can act to promote airway responses in a concentration-dependent manner, possibly through its ability to induce local oxidative stress. Asthmatics have been shown to have a greater sensitivity to SO_2 than non-asthmatics, but the exact mechanisms are yet to be fully understood. Of relevance, the ROS/RNS production within the lung in response to SO_2 exposure can be modified with antioxidant administration, providing insight into the putative mechanisms of SO_2 effects and potential therapeutic applications in the setting of asthma. Furthermore, the airway inflammation resulting from the oxidative stress associated with SO_2 exposure may be of greater magnitude in asthmatics, which may, in turn, be more difficult to resolve, as compared to non-asthmatics. Consideration of these possibilities suggests that enhanced SO_2 effects in asthmatics could be potentially due to their inability to produce necessary amounts of IL-10 to resolve the inflammation resulting from SO_2-induced oxidative stress. Animal studies of SO_2 in specifically targeted systems, such as IL-10 knockout mice and *in vitro* cellular small interfering (si)RNA knockdowns, may provide information necessary to better resolve this prospective link and provide additional therapeutic targets to protect asthmatics from potential pathology associated with the inhalation of SO_2.

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Author Contributions

Conceived and designed the manuscript: ALR, BTA. Wrote the first draft of the manuscript: ALR, BTA. Contributed

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to the writing of the manuscript: ALR, EGB, BTA. Jointly developed the structure and arguments for the paper: ALR, EGB, BTA. Made critical revisions and approved final version: ALR, EGB, BTA. All authors reviewed and approved of the final manuscript.

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