Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation

Review

Antioxidants and Chronic Obstructive Pulmonary Disease

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Abstract

Antioxidants represent an attractive therapeutic avenue for individuals with chronic obstructive pulmonary disease (COPD). Cigarette smoke, the major cause of COPD, contains very high concentrations of gaseous and soluble oxidants that can directly induce cell injury and death. Furthermore, particulate matter in cigarette smoke activates lung macrophages that subsequently attract neutrophils. Both neutrophils and macrophages from the lungs of cigarette smokers continuously release large amounts of superoxide and hydrogen peroxide through the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex. Once individuals with COPD stop smoking, the neutrophilic inflammation in the airways and lung parenchyma persists, as do the markers of oxidative stress. Several animal models of cigarette smoke-induced injury have provided evidence that various antioxidants may prevent inflammation and morphological changes associated with COPD however, evidence of benefit in patients is less abundant. Although oxidants can inactivate alpha-1 antitrypsin and other protective proteins, damage lung tissue, and increase mucus production, they also are essential for killing pathogens and resolving inflammation. This review will examine the pre-clinical and clinical evidence of a role for antioxidants in the therapy of patients with COPD.

Abbreviations: chronic obstructive pulmonary disease, **COPD**; nicotinamide adenine dinucleotide phosphate hydrogen, **NADPH**; chronic granulomatous disease, **CGD**; hydrogen peroxide, **H_2O_2**; hypochlorous acid, **HOC1**; cystic fibrosis transmembrane conductance regulator, **CFTR**; inducible nitric oxide synthase, **iNOS**; N-acetylcysteine, **NAC**; twice daily, **BID**; nacystelyn, **NAL**; 3 times daily, **TID**; Global initiative for chronic Obstructive Lung Disease, **GOLD**; superoxide dismutase, **SOD**; glutathione peroxidase-1, **GPX**; hydrogen, **H_2**; NADPH oxidase, **NOX**; myeloperoxidase, **MPO**

Funding Support: Dr. Cantin is a member of the Fonds de Recherche du Quebec-funded Centre de Recherche Clinique du CHUS, and was supported by a grant from the Canadian Institutes of Health Research.

Date of Acceptance: August 31, 2018

Citation: Vézina FA, Cantin AM. Antioxidants and chronic obstructive pulmonary disease. *Chronic Obstr Pulm Dis.* 2018;5(4):277-288. doi: https://doi.org/10.15326/jcopdf.5.4.2018.0133

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Keywords:

emphysema; alpha-1antitrypsin; N-acetylcysteine; inflammation; cigarette smoke

Introduction

Chronic obstructive pulmonary disease (COPD) is a growing health problem around the world and one of the major chronic health conditions in which disability and death rates are increasing.[1] The economic burden of COPD continues to increase while new therapies are having limited impact on health-related quality of life, respiratory exacerbations or the risk of acquiring COPD. While cigarette smoking is the major cause of COPD, alpha-1 antitrypsin

deficiency leads to pulmonary emphysema and shares several features of acquired COPD in which antioxidants have been studied and shown some promise. Pre-clinical models of emphysema induced with oxidant stress and/or protease-dependent lung damage have also provided insights into the potential for antioxidants as therapies. However, emphysema associated with alpha-1 antitrypsin deficiency also is distinct from acquired COPD. The potential interest of antioxidants in the management of both acquired COPD and emphysema from alpha-1 antitrypsin deficiency are reviewed here.

Beneficial Effects of Oxidants

Oxidants play key physiological roles in the lung, including pathogen killing and resolution of inflammation. Individuals with a lack of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase activity, also known as chronic granulomatous disease (CGD) are susceptible to infections with various pathogens often found in patients with COPD.[2] Oxidants also play an important role in driving the pro-resolution pathways of inflammation by stimulating the orderly removal of spent neutrophils (efferocytosis), and modulating key cysteine residues situated on several regulatory molecules of inflammation (Figure 1).[3-5] The absence of oxidants as observed in individuals with a hereditary absence of NADPH oxidase activity leads to excessive inflammation that never fully resolves.[6,7]

COPD and Oxidative Stress

The major cause of COPD independent of alpha-1 antitrypsin status is cigarette smoking. Cigarette smoke is an abundant source of oxidants derived from both the gaseous and particulate phases. Spin trapping techniques have revealed the presence of 10^{15} radicals per puff, and the tar of cigarette smoke contains a stable semiquinone capable of reducing oxygen to produce superoxide, a direct precursor of hydrogen peroxide.[8,9] Furthermore, smokers inhale 1µg of iron per 25 cigarettes and the smoke itself releases iron from ferritin, giving the lung surface fluid ample iron to generate the toxic hydroxyl radical through the Haber-Weiss and Fenton reactions.[10,11] Oxides of nitrogen present in cigarette smoke react with superoxide to form reactive peroxynitrite.[9] Cigarette smoke alone is sufficient to oxidize alpha-1 antitrypsin and damage DNA.[12,13] Oxidation of alpha-1 antitrypsin reduces its ability to inhibit neutrophil elastase, a major factor in the pathogenesis of COPD. In addition, cigarette smoke activates macrophages and stimulates their proliferation. Activated macrophages from smokers attract neutrophils and release high levels of superoxide and hydrogen peroxide (H_2O_2) through the NADPH oxidase complex.[14] Phagocytes obtained from the lungs of healthy smokers release enough oxidants to oxidize and inactivate alpha-1 antitrypsin.[15] Neutrophils also release myeloperoxidase, which converts H_2O_2 to hypochlorous acid (HOCl), a potent oxidant.[16]

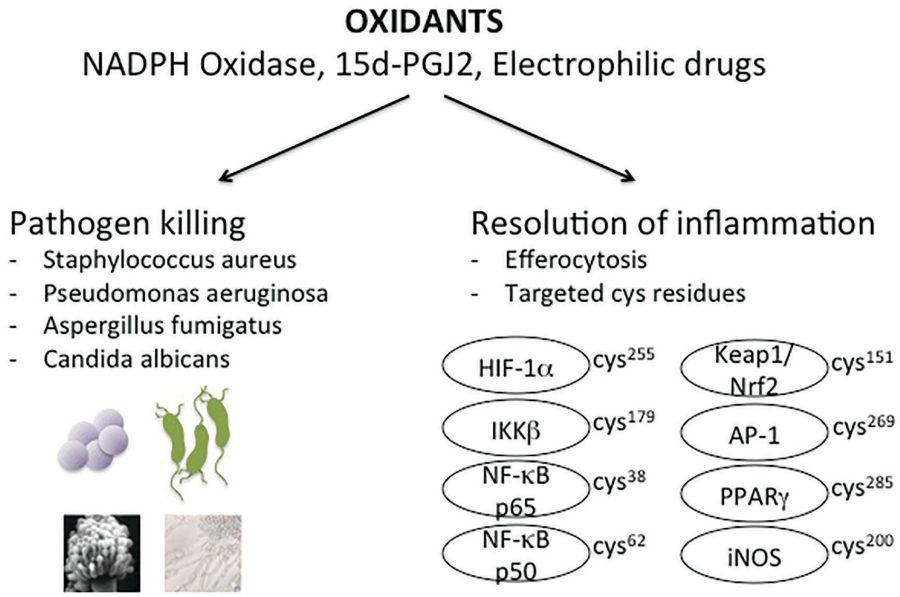
Airway defenses against oxidants include airway surface mucins that can scavenge HOCl and other oxidants,[17] however, oxidant stress markedly increases mucin gene transcription, goblet cell hyperplasia and mucin granule exocytosis.[18] Increased mucus production leads to cough and sputum production, both of which are common symptoms in patients with COPD. Other adaptive mechanisms of the respiratory tract to cigarette smoke-related oxidative stress include increased glutathione synthesis and decreased cystic fibrosis transmembrane conductance regulator (CFTR) activity, both of which have been observed in healthy smokers.[19,20] The increase in mucus production, and the decrease in CFTR activity can precede COPD and persist once disease is established,[21] indicating that the presence of oxidant stress plays a role in the early onset of disease and is an attractive therapeutic target.

Therefore, although oxidants play key roles in pathogen killing and resolution of inflammation, oxidative stress caused by cigarette smoke and macrophage activation contributes to the pathophysiology of COPD by creating a vicious circle that is difficult to stop once started (Figure 2). However, documenting evidence of clinical benefit of antioxidant therapy has been a challenge and innovative antioxidant therapies are yet to be tested in COPD.

Alpha-1 Antitrypsin Deficiency and Oxidative Stress

Among individuals with COPD, those with alpha-1 antitrypsin deficiency have a distinct pattern of oxidative stress characterized by an increase in exhaled breath nitric oxide, accelerated polymerization of

Figure 1. Beneficial Effects of Oxidants



Oxidants, including NADPH oxidase, 15d-PGJ2 (a prostaglandin) and electrophilic drugs, play an important role in controlling infection and resolving inflammation by stimulating the orderly removal of neutrophils (efferocytosis), and modulating key cysteine residues situated on several regulatory molecules of inflammation.

NADPH=nicotinamide adenine dinucleotide phosphate hydorgen

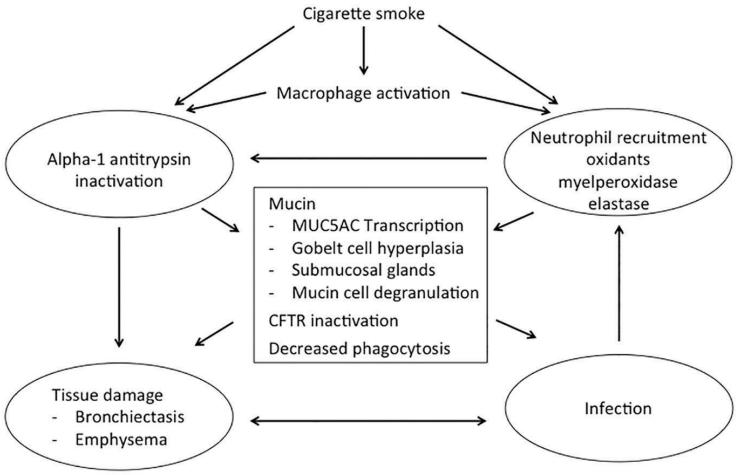
oxidized Z-AT (Glu342Lys) protein which increases inflammation, and decreased serum glutathione and catalase before the appearance of COPD.[22-24] This pro-oxidant profile likely contributes to increased lung damage in individuals with alpha-1 antitrypsin deficiency and suggests that antioxidant therapy represents a reasonable therapeutic objective to explore in non-smokers as well as smokers. The increase in nitric oxide is particularly intriguing since alpha-1 antitrypsin has been shown to inhibit iNOS, nitric oxide release and NF-κB activation, suggesting that alpha-1 antitrypsin replacement therapy or other neutrophil elastase inhibitor therapies may help decrease oxidative stress and inflammation.[25]

Antioxidant Thiol-Based Drugs

Several thiol and non-thiol antioxidants with potential interest in COPD are listed in Table 1. Among the thiol-based drugs, the most extensively studied is N-acetylcysteine (NAC). NAC is a pro-drug with an acetyl group linked to the nitrogen atom of cysteine, thus allowing better stability and absorption of cysteine. Cysteine is a rate-limiting amino acid in the synthesis of glutathione, a major thiol antioxidant. Inhaled NAC is an effective mucolytic drug that reduces sputum viscosity and elasticity, improves mucociliary clearance and modulates inflammatory responses. Furthermore, NAC has both direct and indirect antioxidant properties, which have been extensively assessed in in-vitro and in-vivo studies.[26] However, inhalation of NAC requires a compressor, is associated with a foul odor and can cause bronchospasm.[27] A more convenient and safe delivery of NAC is through the oral route. The usual oral dose of NAC used in studies of COPD is generally 600 mg 2 to 3 times daily. A systematic review of 11 trials in which 2011 patients with chronic bronchitis randomized to NAC or placebo for 3–6 months revealed fewer exacerbations (29% decrease) and a greater number reporting improved respiratory symptoms (64% versus 34%) in patients taking NAC.[28] In contrast, the BRONCUS study in which patients received a daily dose of 600 mg NAC showed no benefit in COPD,[29] whereas in the HIACE and PANTHEON studies in which the dose was 600 mg twice daily (BID), a decrease in the frequency of acute exacerbations was observed with NAC.[30,31] Recently, 3 systematic reviews and meta-analyses have suggested that long-term (6 months or more) NAC at 600 mg BID, may decrease the incidence of respiratory exacerbations in COPD.[31-33] However, it remains unknown whether specific patient populations could benefit more from NAC therapy than others.[34] A recent analysis from the Cochrane Database of Systematic Reviews concludes that NAC likely has a modest beneficial effect on respiratory exacerbations and quality of life in patients with COPD, but that the effect tends be smaller in recent larger studies.[35]

Nacystelyn (NAL) is a lysine salt of NAC. In vitro studies demonstrated that it scavenged H_2O_2 and increased glutathione synthesis twice as effectively as NAC, and reduced H_2O_2 release by polymorphonuclear leukocytes isolated from the blood of smokers with COPD.[36] NAL is soluble at a physiological pH and may represent an improved formulation for cysteine

Figure 2. Potentially Deleterious Effects of Oxidants in the Pathogenesis of COPD



Cigarette smoke can either directly oxidize alpha-1 antitrypsin and induce tissue damage or activate alveolar macrophages to release oxidants. Activated macrophages recruit neutrophils that synthesize more oxidants through NADPH oxidase, and release myeloperoxidase to generate hypochlorous acid and elastase that can overwhelm alpha-1 antitrypsin and increase mucin production. Oxidants and proteases also inactivate CFTR and decrease opsonin-dependent phagocytosis, all of which favor infection. Infection increases neutrophil recruitment thus fueling vicious circles of mucin accumulation (chronic bronchitis and acute exacerbations) and tissue destruction (emphysema).

NADPH=nicotinamide adenine dinucleotide phosphate hydrogen; CFTR=cystic fibrosis transmembrane conductance regulator

delivery and glutathione synthesis, however no clinical trials in COPD patients have been reported.

N-Isobutyrylcysteine, a thiol designed to deliver more free thiol than NAC does, was tested against placebo in 637 individuals with COPD for 6 months, and found to have no effect on respiratory exacerbations.[37] The lack of effect despite improved thiol delivery led the authors to suggest that thiol repletion may not be the mechanism by which NAC reduces respiratory exacerbations in COPD.

Carbocisteine (S-carboxymethylcisteine) is a mucolytic/antioxidant agent widely used in Europe and Asia to treat patients with COPD.[38-40] A multicenter study of 709 patients with COPD in China (PEACE study) treated with placebo or 1500 mg carbocisteine per day for 1 year demonstrated a reduction in the number of acute respiratory exacerbations in the active drug group.[41] An observational study from Naples included 85 COPD patients with at least 1 episode of exacerbation in the previous year, who were treated for 1 year with a daily dose of 2.7 g carbocisteine lysine.[42] At the end of 1 year of carbocisteine therapy, the number of respiratory exacerbations was decreased and the quality of life improved when compared to the previous year. A meta-analysis of carbocisteine use in COPD in 4 studies from China included 1357 patients receiving either placebo or 500 mg carbocisteine 3 times daily (TID) for 1 year.[43] Again, the active treatment group showed a reduction in the number of respiratory exacerbations and an improvement in quality of life, without effect on lung function. Carbocisteine was found to be safe and well tolerated in all studies. The results for NAC and carbocisteine led to a statement in the 2017 Global initiative for Chronic Obstructive Lung Disease (GOLD) guidelines listing these antioxidant/mucolytic drugs as an additional therapy to consider in the treatment of COPD.[44] However, due to the heterogeneity of clinical studies, drug dosing and formulation, as well as difficulty in identifying the target population among those with COPD, the implementation of carbocisteine or NAC in the treatment of COPD has been limited.

Erdosteine contains 2 blocked sulfhydryl groups that after first pass metabolism are converted to 3 metabolites with mucoactive and antioxidant properties that can scavenge free radicals. One of the first clinical studies of erdosteine, the EQUALIFE study was a randomized placebo-controlled trial of 124 patients with COPD assigned to receive either placebo or 300 mg BID erdosteine for 8 months.[45] The results demonstrated an improvement in health-related quality of life, decreased respiratory exacerbations, fewer hospital days and a reduced cost of health care in the active drug group. A meta-analysis of published and unpublished data including patient data provided by the manufacturer examined 15 random controlled trials of 1046 patients who had taken erdosteine for at least 10 days.[46] The authors reported an improvement in respiratory symptoms in the active drug, and few adverse events characterized mostly by gastrointestinal symptoms. A small, short clinical study comparing 4 weeks of erdosteine therapy at either 300 mg BID or 300 mg TID in 24 patients with COPD, demonstrated a decrease in 8-isoprostane levels compared to baseline values.[47] The difference was particularly significant in the high dose group, suggesting an in vivo antioxidant effect. A 1-year randomized placebo-controlled clinical trial of erdosteine in 445 with GOLD stage II/III COPD (the RESTORE study), revealed a 19.4% decrease in the number of respiratory exacerbations in

Table 1. Antioxidants of Potential Interest in COPD

Antioxidant	Mechanism	Clinical trials/ studies
N-acetylcysteine	Cysteine donor	Yes[28,30-33]
Nacystelyn	Cysteine donor	No
N-Isobutyrylcysteine	Cysteine donor	Yes[37]
Carbocisteine	Cysteine donor	Yes[38-43]
Procysteine	Cysteine donor	No
Erdosteine	Mucolytic, antioxidant	Yes[44-47]
Thioredoxin	Oxido-reductase	No
15d-PGJ2	Nrf2 agonist	No
CDDO-Imidazolide	Nrf2 agonist	No
Sulforaphane	Nrf2 agonist	Yes[59]
Chalcones	Nrf2 agonist	No
SOD mimics	Superoxide dismutase	No
Ebselen	Glutathione peroxidation	No
Molecular hydrogen (H2)	-OH radical scavenger	No
Celastrol	NOX inhibitor Nrf2 agonist	No
2-thioxanthine	MPO inhibitor	No
Diet (fruits & vegetables)	Multiple antioxidants	Yes[82]

the group on active drug, and no increase in adverse events was reported.[48]

Taken together these studies strongly suggest that the addition of thiol or thiol-related antioxidant/ mucoactive oral drugs at 300-600 mg BID to the current COPD therapeutic regimen can reduce the number of respiratory exacerbations and may improve health-related quality of life while adding very few adverse events.

Fudosteine is a cysteine derivative with better bioavailability than NAC, and has been shown to increase cellular cysteine, decrease goblet cell hyperplasia, inhibit MUC5AC mucin secretion and gene expression in the rat airway. There are currently no published clinical trials of fudosteine in COPD.[49-51]

Procysteine (cysteine l-2-oxothiazolidine-4-carboxylic acid) is a cysteine donor and can enhance the synthesis of cellular glutathione. Acute exposure to cigarette smoke decreases available glutathione and macrophage-dependent efferocytosis. Efferocytosis, a key anti-inflammatory mechanism is deficient in the lungs of patients with COPD. Oral procysteine increases lung glutathione and efferocytosis in smoke-exposed mice, suggesting that further studies of procysteine in COPD may be warranted.[52]

Thioredoxin is a 12 kDa oxido-reductase enzyme capable of donating electrons to help reduce oxidized proteins, ribonucleotides and cell signaling molecules including p38 mitogen-activity protein kinase, NFkB and phosphatidylinositol 3 kinase.[53] Thioredoxin also regulates pathways involved in autophagy, an important process in the development of emphysema. Intra-peritoneal injection of thioredoxin in mice decreases pulmonary neutrophil inflammation and decreases the severity of poly(I:C)-induced emphysema.[54] There are no clinical trials of thioredoxin in COPD.

Agonists of Nuclear Factor Erythroid 2-Related Factor 2

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that interacts with Keap1 and is ubiquitinated by Cullin 3 in the cytoplasm prior to its degradation in the proteasome. Upon exposure to electrophilic molecules, the conformation of Keap1 is altered. Nrf2 then enters the nucleus and binds the antioxidant response element of specific genes involved in a concerted antioxidant response.[5] Agonists of Nrf2 markedly increase glutathione synthesis. The importance of this antioxidant pathway is illustrated in Nrf2 knockout mice in which lung neutrophil inflammation and pulmonary emphysema were evident as early as 8 weeks after cigarette smoke exposure, whereas wild-type mice showed no lung changes at 16 weeks.[55] Several endogenous and exogenous Nrf2 agonists have been identified. Selenium supplementation is of particular interest since it increases macrophage synthesis of the electrophilic cyclopentenone 15d-PGJ2.[56-58] Not only is 15d-PGJ2 a potent Nrf2 agonist, that markedly increases cellular antioxidants, but it also has potent anti-inflammatory properties related to its capacity to S-alkylate several key cysteine residues in proteins regulating inflammatory pathways including NFκB and PPARγ.[58] While 15d-PGJ2 can protect mice against lethal pulmonary inflammation, the molecule is unstable and poorly soluble making it less favorable for therapy. However, other molecules with similar properties have been developed and investigated in pre-clinical studies, including CDDO (2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid), sulforaphane and chalcones.

CDDO-imidazolide administered during the period

of cigarette smoke exposure has been shown to protect mice against pulmonary emphysema through a mechanism that requires Nrf2.[59] However, the clinical efficacy of CDDO-Im has not been explored in clinical trials, and it is unknown whether CDDO-Im would have any effect in patients with established emphysema who are no longer smoking.

Sulforaphane, a naturally occurring isithiocyante found in broccoli sprouts and cruciferous vegetables is a potent Nrf2 agonist. A 4-week randomized parallel placebo-controlled trial of 0, 25 or 150 μmol oral sulfurophane failed to show any changes in alveolar macrophage and bronchial epithelial cell expression of genes encoding antioxidants, or in markers of inflammation in a trial of 89 patients with COPD.[60]

Chalcones (1,2-diphenyl-2-propen-1-one) are synthesized by several food plants and comprise part of a healthy diet. Some electrophilic chalcones such as isoliquiritigenin (licorice roots) and xanthohumol (hops) have been shown to decrease pulmonary inflammation caused by LPS and the influenza virus, but no studies have been reported in COPD.[61,62]

Superoxide Dismutase and Glutathione Peroxidase

Salen-metal compounds are superoxide dismutase (SOD) mimetics. Macrocyclic Mn(II) pentaazamacrocyclic ligands such as M40419 have been shown to decrease oxidative stress and prevent emphysema induced in rats by vascular endothelial growth factor receptor blockade.[63] Other SOD mimetics such as the manganese metaloporphyrin AEOL-10113 decrease murine airway inflammation and hyperreactivity,[64] whereas AEOL-10150 decreases cigarette smoke-induced pulmonary inflammation.[65] These compounds have not been studied in patients with COPD.

Ebselen

Glutathione peroxidase-1 (GPX) is a member of the selenium-dependent protein family that catalyzes the reduction of hydrogen peroxide, and as such it plays a key role in preventing cigarette smoke-induced inflammation in murine lungs.[66] Interestingly, red blood cell GPX levels correlate with pulmonary function (forced expiratory volume in 1 second) in patients with COPD.[67] Plasma levels of selenium are low in patients with COPD, and a similar trend towards low plasma selenium has been reported in individuals homozygous for the ZZ alpha-1 antitrypsin genotype.[57,68] Ebselen, an organoselenium molecular mimic of GPX has been shown in several lung inflammation models in mice including cigarette smoke exposure, to protect against pulmonary inflammation.[69-71] Although the preclinical data is promising, there are no clinical trials of ebselen in COPD.

Hydrogen

Hydrogen (H2) has been found to be a potent antioxidant, capable of reducing hydroxyl radical and preventing cell damage.[72] Hydrogen gas has been advocated as a novel and safe antioxidant strategy.[73] Further studies have determined that hydrogen-rich water supplementation in SMP30 knockout mice exposed to cigarette smoke prevents the appearance of emphysema.[74] Mice exposed to cigarette smoke for 8 weeks and treated with hydrogen-rich pure water showed lower lung compliance, decreased levels of oxidative DNA damage markers such as phosphorylated histone H2AX and 8-hydroxy-20-deoxyguanosine, and lower lung senescence markers such as cyclin-dependent kinase inhibitor 2A, cyclin-dependent kinase inhibitor 1, and b-galactosidase. Therapy was well tolerated in mice, but no clinical trials of hydrogen-rich pure water have been reported.

NADPH Oxidase Inhibition

Celastrol is an electrophilic triterpenoid derived from the root of the Thunder god vine Trypterygium wilfordii, that has a dual antioxidant mechanism. First, its electrophilic carbon makes it a potent Nrf2 agonist that can induce the synthesis of key cellular antioxidants.[75] Second, celastrol is a NADPH oxidase (NOX) inhibitor.[76] One of the sources of oxidant stress in the lung of cigarette smokers and individuals with COPD is the synthesis of superoxide, hydrogen peroxide and other downstream oxidants by activated bronchial and alveolar phagocyte.[77] Mice that overexpress ECSOD or NOX-deficient mice are each protected against oxidative damage and lung inflammation associated with cigarette smoke.[78] While it may be tempting to conclude from these studies that NOX inhibition with celastrol or other drugs may represent an interesting therapeutic goal in COPD, it is important to recall that

individuals with genetically defined NOX deficiencies are afflicted by life-threatening bacterial infections.[2]

Myeloperoxidase Inhibition

Myeloperoxidase (MPO) is present in the azurophilic granule of the neutrophil and comprises 5% of the cell's dry weight.[79] Its physiological role is thought to be related to the killing of pathogens and the resolution of inflammation. Individuals who are deficient in MPO are generally healthy but have a mildly increased risk of life-threatening infections and inflammatory diseases.[80] MPO inhibition has been studied in a chronic guinea pig model of cigarette smoke-induced emphysema using 2-thioxanthine (AZ1), an MPO inhibitor developed by AstraZeneca. Animals treated with the MPO inhibitor up to 3 months after the initiation of cigarette smoke exposure, were protected against morphologic changes characteristic of emphysema.[81] However, the potential consequences of chronic MPO inhibition in individuals with COPD who are already at an increased risk of pulmonary inflammation and infection are unknown.

Diet and COPD

The most significant source of antioxidants in daily life is not drugs or nutritional supplements but our diets. Although several specific dietary natural products have been isolated, purified and studied in the pathogenesis of COPD,[82] it is possible that the combination of these antioxidants provided in a healthy diet is the best antioxidant approach to minimize the nefarious consequences of emphysema. This concept is supported by the recent prospective Cohort of Swedish Men study in which 44,335 volunteers aged 45–79 years old were followed for 13. 2 years.[83] Of these men, 1918 incidents of COPD were documented, allowing the investigators to study current smokers, ex-smokers and never smokers with respect to their consumption of fruits and vegetables. In current and ex-smokers, (but not in nonsmokers), each additional daily serving of fruits and vegetables decreased the risk of COPD by 8% and 4% respectively. There currently is no other study of antioxidants that has shown nearly as great an impact on the risk of COPD in smokers and ex-smokers, and these observations argue strongly in favor of including a comprehensive assessment and follow-up of dietary habits in smokers and ex-smokers at risk of developing COPD.

Summary and Recommendations

Based on the studies of antioxidant and mucolytics, various respiratory associations and bodies have made the following recommendations:

- GOLD Executive Summary 2017[44]: "Regular treatment with mucolytics such as carbocysteine and N-acetylcysteine may reduce exacerbations and modestly improve health status in patients not receiving inhaled corticosteroids."
- European Respiratory Society/American Thoracic Society 2017[84]: In "COPD with moderate or severe airflow obstruction and exacerbations despite optimal inhaled therapy, we suggest treatment with an oral mucolytic agent to prevent future exacerbations".
- American College of Chest Physicians and Canadian Thoracic Society 2015[85]: "N-acetylcysteine treatment for patients with moderate to severe COPD and a history of 2 or more exacerbations during the previous 2 years."

Conclusions

COPD is clearly associated with an excessive lung oxidant burden and the rationale for exploring antioxidant therapies in this patient population is strong. Sufficient clinical evidence is available to recommend the use of NAC or carbocisteine as an addition to current therapies in certain patients with COPD, at least in the hope of reducing the number of respiratory exacerbations and possibly improving the health-related quality of life. In addition to the recommendations already summarized by various lung associations, we would strongly recommend that consideration be given to include dietary interventions focused on increasing the fruit and vegetable intake as an important and immediately applicable approach to increasing antioxidants in individuals who have or are at risk of developing COPD.

Despite the identification of many potential targets of antioxidant therapy, and abundant pre-clinical data, few antioxidant agents have undergone formal trials to assess clinical benefit in COPD. Even fewer have made it to the bedside. Among the several barriers to clinical trials of antioxidants in COPD are clinical trial design for such a heterogeneous patient population, cost of large-scale clinical trials, selection of efficacy measures, and drug formulation. However, sufficient

pre-clinical and clinical data exist to justify well-designed clinical trials of antioxidants in COPD.

Declaration of Interest

The authors have no conflicts of interest to declare.

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