Research Article

A BRIEF REVIEW ON EFFECT OF OXIDATIVE STRESS ON VARIOUS DISEASES INCLUDING A LUNG DISEASES

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Abstract

Oxidative stress occurs when the generation of free radicals and active intermediates in a system exceeds the system's ability to neutralize and eliminate them. Oxidative stress is the result of an imbalance in pro-oxidant/antioxidant homeostasis that will leads to the generation of toxic reactive oxygen species (ROS), such as hydrogen peroxide, organic hydro peroxides, nitric oxide, superoxide and hydroxyl radicals. Information suggests the importance of oxidative damage of tissue and cellular components as a primary or secondary causative factor in many diseases and aging processes. The various types of disease discussed in brief with is review article.

Keywords: Oxidative stress, cancer diseases

I. Introduction

Oxidative stress is characterized by the imbalance between the oxidants and antioxidants defense. The acute or chronic exposure of oxidants molecule leads to generation of ROS (Reactive oxygen species), and RNS (Reactive nitrogen species). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) play a crucial roles in regulation of cell survival. Normally, moderate levels of ROS/RNS may function as signals to promote cell proliferation and survival, where as a sudden excessive and prolonged surge of ROS/RNS alter the redox homeostasis can induce cell death. The result is excessive cellular/tissue damage that results in chronic inflammation and destruction of normal tissue ADDIN EN.CITE The lung, owing to its extensive surface area and blood supply, is the only organ in the entire human architecture which has the greatest exposure to atmospheric oxygen and other environmental toxicants. Hence, the lung is susceptible to oxidative injury by virtue of myriads of reactive forms of oxygen species. ROS and RNS are highly unstable due to unpaired electrons that are capable of initiating oxidation (1), (2).

Various sources of oxidant.

The occurrence of oxidative stress in lung is enhanced due to the numerous environmental, chemical, and physical agents. This may include mineral dust ozone, nitrogen oxides, sulphur dioxide, ultraviolet and ionizing radiation and the most important tobacco smoke.

Outdoor air quality is an increasing concern globally with expanding industrial and transportation emissions. The World Health Organization (WHO) has declared that, p **Particulate Matter (PM)** in ambient outdoor air affects more people than any other

pollutant. Chronic exposure to particles contributes to the risk of developing or dying from serious disease (WHO 1).

Figure 1: Environmental pollution

The effects of PM on health occur at levels of exposure currently being experienced by most urban and rural populations in both developed and developing countries. Burning fuel results in two phases of emissions. In addition to the "particulate phase," there is a "gas phase" containing air pollutants such as benzene, formaldehyde, polycyclic aromatic hydrocarbons (PAHs), and other chemicals, which also contribute to disease (EPA 1, EPA 2). The combustion of fossil fuel for electricity and transportation, especially coal and diesel, are major contributors to outdoor air pollution (3), (4).

Ambient air pollution, containing particulate matter smaller than aerodynamic diameter of 2.5 μm (PM2.5), has gained particular attention in recent years as a causative factor in the increased incidence of respiratory diseases, including lung cancer. Particulate Matter (PM) is composed of very small, solid particles, formed from the incomplete burning of fossil fuels such as coal, diesel, gasoline, and biomass. PM consist of a complex mixture of soot, black carbon, absorbed water, aerosolized sulfuric acid droplets, other acids, nitrogen, sulfur, metals, and other toxic substances. which are absorbed by the sponge-like particles and carried by them deeply into the smallest compartments of the lung (alveoli), where they gain direct access to the bloodstream and may then contribute to various diseases in organs distant from the lungs, including the fetal plecenta (5) (6).

Airborne PM is an important pollutant of urban atmosphere and has been linked to adverse health effects of the respiratory system. The ability of respirable particles or fibrous dusts to penetrate the respiratory system and reach the lung alveoli in order to generate ROS and other oxidants or free radicals is suggested to be the main factor involved in their pathogenic potential. There is abundance of scientific evidence for ROS involvement in lipid peroxidation, DNA mutations and protein (enzyme) oxidative damage (7).

Studies have investigated the effect of or ambient air pollutants in terms of oxidized DNA nucleobases. In nuclear and mitochondrial DNA (mtDNA) a free radical-induced oxidative lesion has been used widely as a predominant biomarker for oxidative stress. 8-Oxo-7,8-dihydroguanine (8-oxoGua) can be measured quantitatively by HPLC and

GC-MS in animal and in human biomonitoring studies (8), (9).

Apart from the particulate matter **Cigarette smoking**, is another environmental hazard, also delivers oxidants and free radicals to the lungs which damage the lungs and responsible for the so many life threating lung disorders. Tobacco smoke has been reported to contain over 6000 chemicals, more than 70 of which have been shown to be carcinogenic. These include arsenic, benzene, benzo(a)pyrene, cadmium, and formaldehyde). When inhaled, these compounds contribute to DNA damage, resulting in the mutation of genes involved in controlling cellular growth

Cigarette smoke contains many oxidants and free radicals, both in the gas and the tar phase. A direct consequence of cigarette smoking and inhalation of airborne pollutants is lung damage and elevated inflammatory responses in the lungs, and are implicated in the pathogenesis and exacerbations of chronic obstructive pulmonary disease (COPD). In the gas phase, the cigarette smoke comprises of high concentrations of oxidants/free radicals (>1015 molecules/puff) [9] short-lived oxidants such as (O_2) and NO. Nitric oxide and (O_2) immediately react to form highly reactive ONOO_ molecule.

The tar phase of cigarette smoke contains organic radicals, such as long-lived semiquinone radicals, which can react with molecular oxygen in a redox dependent manner to form (O_2), OH_ and et al., H_2O_2 The aqueous phase of cigarette smoke condensate may undergo redox recycling for a considerable period of time in the epithelial lining fluid (ELF) of smokers (The tar phase is also an effective metal chelator wherein iron is chelated to produce tar-semiquinone + tar-Fe2+, which can generate H_2O_2 continuously (It is of much importance to note that cigarette smoke has been recently reported to irreversibly modify GSH levels in airway epithelial cells; a basic mechanism which may underlie cigarette smoke mediated oxidant and inflammatory lung damage (10)

Another potent oxidant source is **ozone** which is (O_3) is a gas molecule composed of three oxygen atoms. Often called “smog,” ozone is harmful to breathe. Ozone aggressively attacks lung tissue by reacting chemically with it. It is potent oxidant which cause cellular damage by lipid peroxidation as weel as loss of functional groups on biomolecules. Inhalation of ozone may lead to an increase in neutrophil numbers, increased airway responsiveness and reduced pulmonary function in normal subjects This has been linked to neutrophil infiltration into the airway epithelium (11).

Pulmonary Disease Occurred by Oxidative Stress

Chronic obstructive pulmonary disease

The development and progression of chronic obstructive pulmonary disease (COPD) have been associated with increased oxidative stress or reduced antioxidant resources Chronic obstructive pulmonary disease (COPD) is a condition characterized by progressive and largely irreversible airway obstruction and an influx of inflammatory cells into the lungs. “Oxidative stress damages and impairs the functioning of several kinds of proteins, harming lung physiology in ways that can induce COPD. The harmful effects include oxidative inactivation of antiproteases and surfactants, excessive secretion of mucus, membrane lipid peroxidation, mitochondrial respiration, alveolar epithelial injury, remodeling of the extracellular matrix, and apoptosis. Exercise causes increased oxidative stress in COPD patients, as in healthy people. But additional

oxidative stress occurs in COPD patients, because oxidative stress causes inflammation in turn causes more oxidative stress. This cycle occurs because oxidation causes various protein dysfunction, and that hinders the operation of function that restore a healthy oxidant/antioxidant balance (12).

Lung cancer

Lung cancer (also known as carcinoma of the lung) is a disease characterized by uncontrolled cell growth in tissues of the lung. If left untreated, this growth can spread beyond the lung by process of metastasis into nearby tissue or other parts of the body. Most cancers that start in the lung, known as primary lung cancers, are carcinomas that derive from epithelial cells. The main types of lung cancer are small-cell lung carcinoma (SCLC), also called oat cell cancer and non-small-cell lung carcinoma (NSCLC). The most common symptoms are coughing (including coughing up blood), weight loss, and shortness of breath and chest pain. The majority of lung cancers are classified as either non-small cell lung cancer or small cell lung cancer, which get their names because of the appearance of the cancer cells under a microscope. Non-small cell lung cancer accounts for 80% of lung cancers (13), (14), (1).

Reactive oxygen species have been suggested to stimulate oncogenes such as Jun and Fos. Overexpression of Jun is directly associated with lung cancer. In lung cancers, p53, which is associated with the produc- tion of ROS, is often mutated and defective in inducing apoptosis. When mutated, p53 accumulates in the cyto- plasm and functions as an oncogene Modification of proteins and lipids may increase the risk of mutagene- sis, through formation of genotoxic lipid peroxidative by-products that react with DNA, oxidative modification of DNA polymerase or inhibition of DNA repair enzymes (15), (16).

Asthma

Asthma is a disease characterized by airway chronic inflammation and bronchial hyperactivity, involving the imbalance of oxidative and antioxidative agents. In people susceptible to asthma, this inflammation causes the airways to narrow periodically.This narrowing, in turn, produces wheezing and breathlessness that sometimes causes the patient to gasp for air. Obstruction to air flow either stops spontaneously or responds to a wide range of treatments, but continuing inflammation makes the airways hyper-responsive to stimuli such as cold air , exercise dust mites, pollutants in the air, and even stress and **.**

There is strong evidence that an imbalance between the reducing and oxidizing systems favoring a more oxidative state is present in asthma. Endogenous and exogenous reactive oxygen species, such as superoxide anion, hydroxyl radical, hypohalite radical, and hydrogen peroxide, and reactive nitrogen species, such as nitric oxide, peroxynitrite, and nitrite, play a major role in the airway inflammation and are determinants of asthma severity. Asthma is also associated with decreased antioxidant defenses, such as superoxide dismutase, catalase and Glutathione.

Many observations suggest that oxidative stress plays an important role in the pathogenesis of asthma. In the air- way, losing control of oxidants may bring about initiation of Th2-dominant immunity instead of inducing immune tolerance in the initial phase of development of airway allergic inflammation Furthermore, enhanced oxidative stress may contribute to the progression or perpetuation of existing airway

inflammation through enhanced airway hyper responsiveness, stimulation of mucin secretion, and induction of various proinflammtory chemical mediators all of which are believed to be related to severe asthma Higher incidences of bronchial asthma have been reported in areas with air pollution, which is a representative stimulus among exogenous oxidants Reduced intake of foods containing antioxidants is also related to the increased incidence of asthma[19] .Increased oxidative stress in asthmatic patients is also related to suppressed pulmonary function. showed that increased oxidative stress in the airway precedes the development of allergic inflammation, airway hyperresponsiveness, and other pivotal features of asthma such as enhanced mucus secretion. Therefore, it is strongly suggested that an increased level of ROS acts as a critical contributor to the induction of allergic airway inflammation. Control- ling intracellular oxidative stress with appropriate timing, as opposed to simply focusing on the reduction of oxida- tive stress, is important for effectively managing of asthma (17).

Cystic fibrosis

Cystic fibrosis is a lethal autosomal recessive condition caused by a defect of the transmembrane conductance regulator gene that has a key role in cell homeostasis. A dysfunctional cystic fibrosis transmembrane conductance regulator impairs the efflux of cell anions such as chloride and bicarbonate, and also that of other solutes such as reduced glutathione. This defect produces an increased viscosity of secretions together with other metabolic defects of epithelia that ultimately promote the obstruction and fibrosis of organs. Recurrent pulmonary infections and respiratory dysfunction are main clinical consequences of these pathogenetic events, followed by pancreatic and liver insufficiency, diabetes, protein-energy malnutrition, etc. This complex comorbidity is associated with the extensive injury of different biomolecular targets by reactive oxygen species, which is the biochemical hallmark of oxidative stress. These biological lesions are particularly pronounced in the lung, in which the extent of oxidative markers parallels that of inflammatory markers between chronic events and acute exacerbations along the progression of the disease. Herein, an abnormal flux of reactive oxygen species is present by the sustained activation of neutrophils and other cystic fibrosis-derived defects in the homeostatic processes of pulmonary epithelia and lining fluids. A sub-optimal antioxidant protection is believed to represent a main contributor to oxidative stress and to the poor control of immuno-inflammatory pathways in these patients. Observed defects include an impaired reduced glutathione metabolism and lowered intake and absorption of fat-soluble antioxidants (vitamin E, carotenoids, coenzyme Q-10, some polyunsaturated fatty acids, etc.) and oligoelements (such as Se, Cu and Zn) that are involved in reactive oxygen species detoxification by means of enzymatic defenses. Oral supplements and aerosolized formulations of thiols have been used in the antioxidant therapy of this inherited disease with the main aim of reducing the extent of oxidative lesions and the rate of lung deterioration (18).

Pulmonary fibrosis

Pulmonary fibrosis is a respiratory disease in which scars are formed in the lung tissues, leading to serious breathing problems. Scar formation, the accumulation of excess fibrous connective tissue (the process called fibrosis), leads to thickening of the walls, and causes reduced oxygen supply in the blood. As a

consequence patients suffer from perpetual shortness of breath.

In some patients the specific cause of the disease can be diagnosed, but in others the probable cause cannot be determined, a condition called idiopathic pulmonary fibrosis. There is no known cure for the scars and damage in the lung due to pulmonary fibrosis.

Pulmonary fibrosis is the end result of a diverse group of lung disorders. Although there are multiple initiating agents for pulmonary fibrosis, including toxins, fibres/ particles, autoimmune reactions, drugs and radiation, the aetiology of the majority of cases of pulmonary fibrosis is unknown. Several studies have suggested that oxidant-antioxidant imbalance in the airways plays a critical role in the pathogenesis of idiopathic pulmonary fibrosis (IPF). In addition, oxidants may contribute to the development of pulmonary fibrosis due to their effects on the production of cytokines and growth factors such as TGF-β, a key regulator of aberrant repair mechanisms that are characteristic of many fibrotic diseases including IPF. There are several potential interactions between TGF-β and oxidants/antioxidants in the lung. TGF-β not only induces ROS production by activation of NADPH oxidases and/or mitochondrial dysfunction, but also de- creases natural cellular antioxidant production through decreased expression of both catalase and mitochondrial SOD. Increased levels of oxidized proteins have been reported in human subjects with IPF. Some studies have reported that various antioxidant enzyme systems protect against lung fibrosis. But IPF subjects also have lower antioxidant capacity than healthy subjects. Thus, oxidants and TGF-β seem to interact to enhance the fibrotic response in the lungs (19).

Conclusion

Therefore the development of dosage form that is liposomal dry powder inhaler may provide increase clinical value GSH in terms of bioavailability, patient compliance and duration of therapeutic effect. Administration of drugs directly to the lungs via inhalation allows regional drug delivery to the lungs and airways with smaller doses and fewer systemic effects. There is now increasing evidence to support the role of inhaled therapeutics in the treatment of various lung diseases. So DPI formulation would increase the concentration of drug at target site and liposomes would protect drug from rapid enzymatic degradation by glutamyl-trans-peptidases and -glutamyl-cyclo-transferases and also the lipids are integral part of lung, so it its clearance from lung would also be lesser than simple DPI formulation.

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