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REVIEW ARTICLE

Cigarette Smoke-induced Oxidative Stress: A Systematic Review

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ABSTRACT

In the present review, oxidative stress through free-radical generation in cigarette smokers has been widely investigated. Cigarette smoke exposure is a risk factor for human being as well as animals. Cigarette smoke exposure is known to contribute to excess reactive oxygen species generation, the role of oxidative stress and inflammation in Human. They cause lipid peroxidation, oxidation of proteins and damage to mainly lung, and other tissues. The findings obtained in this review work provide some clues for the impact of cigarette smoking.

Keywords: Antioxidants, Cigarette smoke, Free radicals, Oxidants, Oxidative stress

INTRODUCTION

Smoking is a major public health problem which is responsible for large number of preventable health problems. The world health organization estimates that the globally the yearly death toll as a result of tobacco use is currently 6 million. This is expected to rise to 7 million by 2020 and to more than 8 million a year by 2030. It is predicted that by the end of the 21st century, tobacco will have killed one billion people.

At present, almost 1.3 billion (10^9) people smoke cigarettes worldwide: About 1.1 billion men and 230 million women.[1] Nearly two-thirds of the world's smokers live in just ten countries: Bangladesh, Brazil, China, Germany, India, Indonesia, Japan, The Russian Federation, Turkey, and The United States, which collectively comprise about 58% of the global population. Smokers inflict damage not just on themselves but also on others, through second-hand smoke. Smoking was once predominant in the developed world but this trend is changing rapidly. At present, 50% of males in developing countries smoke, compared with only 35% of males in developed countries. Three-quarters of all tobacco users are now in developing countries and they consume nearly 60% of the 5700 billion cigarettes worldwide smoked each year. Over the next 25 years, total cigarette consumption will rise by 60% in countries with medium levels of human development and by 100% in countries with low levels of human development. This latter group of nations will by then consumes more tobacco than either medium or highly developed countries. One hundred million deaths were attributed to tobacco during the 20th century, mostly in developed countries. Given current patterns of consumption, 1 billion deaths due to tobacco are expected this century, but now mostly in developing countries. Half of these deaths will be among those in middle-age (35–69 years old), with harmful effects on national economies. Tobacco is the second leading cause of death in developed and low mortality developing countries, and sixth in high mortality developing countries. Tobacco also accounts for a large portion of the disease burden

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in developing countries, and is currently ranked fourth in the world in its contribution to years of life lost. As poverty has fallen and economies have grown, the major transnational tobacco companies have expanded their influence into the developing world.

PRESENT SMOKERS IN INDIA

India is a diverse country, with marked regional variation in lifestyles. Among adults, most deaths are from respiratory, cardiovascular, or pulmonary disease or from tuberculosis; the death rates from these diseases can be increased by smoking.[2] At present, tobacco users in India approximate 274.9 million, with 163.7 million being users of smokeless tobacco, 68.9 million smokers, and 42.3 million users of both smoking and smokeless tobacco.[3] The prevalence of overall tobacco use among males is 48% and that among females are 20%. Nearly two in five (38%) adults in rural areas and one in four (25%) adults in urban areas use some form of tobacco. The prevalence of smoking among males is 24% whereas the prevalence among females is 3%. The problem is of particular concern in India, where tobacco-related mortality is among the highest in the world. According to the current data, 47% of the Indian males and 14% of the Indian females are tobacco users, resulting in 13.3% of total deaths due to tobacco by 2020.[4] Nearly 8–9 lakh people die every year in India due to diseases related to tobacco use.[4] Majority of the cardiovascular diseases, cancers and chronic lung diseases are directly attributed to tobacco consumption. Almost 40% of tuberculosis deaths in the country are associated with smoking.[5]

India is the second largest consumer of tobacco products and third largest producer of tobacco in the world. To facilitate the implementation of the tobacco control laws and to bring about greater awareness regarding harmful effects of tobacco and fulfill obligation(s) under the WHO Framework Convention on Tobacco Control (WHO), the Government of India has launched the National Tobacco Control Programme in the country. The Adult Tobacco Survey is an important component of the country's comprehensive tobacco control program and reflects an efficient and systematic surveillance mechanism to monitor the tobacco epidemic through collection of baseline data and study of key tobacco control indicators.

APOPTOSIS AND CIGARETTE SMOKING

Apoptosis is a basic physiological process whereby tissues remove unwanted or redundant cells without inflammatory process. It has been observed in many different tissues and is regulated by numerous internal and external signals. In addition, it has been hypothesized that hormones, growth factors, and nutrients may influence the initiation, the progression or prevention and suppression of apoptosis. A number of toxic substances and pollutants may cause apoptosis. Apoptosis or programmed cell death represents an alternative pathway for cell death in the setting of critical illness.[6]

Alveolar epithelial cells are the lung's first line of defense against the external environment. These cells also produce surfactants to reduce surface tension, release cytokines to regulate inflammation, generate growth factors and matrix proteins to promote repair processes, and release proteinases, and proteinase inhibitors to regulate the turnover of alveolar matrix proteins. When injured alveolar epithelial cells participate in repair processes by initiating recruitment, proliferation, and differentiation into new alveolar epithelial cells. Therefore, alterations in alveolar epithelial cells may cause architectural and functional disruptions in the alveolar epithelium. In this context, exposure to cigarette smoke (CS) may induce an increase in epithelial permeability, a decrease in surfactant production, inappropriate generation of inflammatory cytokines, and growth factors and an increased risk of lung cancer.

However, the most deleterious effect of CS on alveolar epithelial cells is cell death, that is, either apoptosis or necrosis. Cell death induced by CS exposure can largely be accounted for by an enhancement in oxidative stress. Cigarette smoke-induced oxidative damages in alveolar epithelial

cells ultimately cause cell death.[7] The type of cell death, either apoptosis or necrosis, depends on the magnitude of CS exposure. There are two possible pathways of cell death: Necrosis and apoptosis. The first process is associated with the effect of hazardous agents and circumstances resulting in the disturbance of cell membrane integrity (because of damage or pore-formation) and isolation of inner cellular contents from the extracellular matrix. The second process is an active realization of the cellular death program. Apoptosis may be caused by signals from outside of cells which are not toxic or destructive. Therefore, apoptosis has been called the "suicide" of the cell. The characteristic morphological changes in cells undergoing apoptosis were first described by pathologists examining tumor sections.[8] They include cell shrinkage, plasma membrane blebbing and a series of nuclear changes, including chromatin condensation, and nuclear breakdown, resulting in the release of nuclear fragments. Almost all smokers have an accumulation of macrophages in the terminal airways of the lung. Smokers' alveolar macrophages are characterized by the presence of many vacuoles containing pigmented cargo, cellular shrinkage, cell surface smoothing, and nuclear compaction.

CIGARETTE SMOKING AND OXIDATIVE STRESS

Cigarette smoking contains numerous compounds and diverse metals, many of which are oxidants and pro-oxidants, capable of producing free radicals and enhancing the oxidative stress *in vivo*.[9] Cigarette smoke is a complex mixture of many toxic substances. There are generally two types of smoke: Mainstream smoke is the smoke inhaled by the smoker, and sidestream smoke (a main component of environmental tobacco smoke) is the smoke given off from the burning end of the cigarette during intervals between puffs. Both smokes are complex mixtures of particulate matter, volatile acids, and gases. An imbalance between the antioxidant capacity and the production of reactive oxygen species leads to oxidative stress, which is associated with the pathogenesis of several human diseases.[10] Oxidative stress induces damage to proteins, DNA, and lipids, which may cause direct lung injury or induce a variety of cellular responses through the generation of secondary metabolic reactive species.[11] Chronic exposure to CS is associated with a decline in antioxidant defenses, both enzymatic and non-enzymatic, through their continuous depletion in response to the oxidative burst. Oxidative damage to cellular components occurs when the production of ROS overwhelms the cell's antioxidant defenses and leads to lipid peroxidation and decreased tissue antioxidant levels. Numerous studies have shown that CS generates oxidative stress in various animal models.[12-14]

OXIDANTS AND CIGARETTE SMOKE

Oxidative stress in cells and organisms is caused by the presence of ROS, including hydroxyl radicals (OH), superperoxide, hydrogen peroxide (H_2O_2), and singlet oxygen. Cells or organisms having an inordinately high level of ROS are said to be under oxidative stress. ROS are generated inadvertently in the mitochondria of all cells concomitant with the synthesis of ATP. ROS arise due to oxygen that escapes complete reduction. Other *in vivo* sources of ROS include inflammatory responses and detoxification processes. Short-lived oxidants, such as superoxide anion (O_2^-) and nitric oxide (NO), are predominantly found in the gas phase of CS. NO· and O_2^- immediately react to form the highly reactive and toxic peroxynitrite (ONOO−) molecule.

The semiquinone radicals in the tar phase of cigarette can reduce oxygen to produce ROS, such as $O_2^{-\cdot}$, ·OH, and H_2O_2.[15] Oxidants present in CS can further augment alveolar macrophage production of ROS and a host of other mediators, some of which are chemotactic and recruit neutrophils and other inflammatory cells into the lungs. Both neutrophils and macrophages, which are known to migrate in increased numbers into the lungs of CSs, compared with nonsmokers, can generate ROS via the activation of NADPH oxidases.[16,17]

MECHANISMS OF FREE RADICAL-INDUCED INJURY FROM CIGARETTE SMOKING

Despite the large body of epidemiological evidence that exists today in establishing a strong correlation between smoking and morbidity and mortality, the exact molecular and biochemical mechanisms of smoke-related disease remain unclear. Recent findings, however, suggest that lung damage resulting in respiratory dysfunction, and induction of carcinogenesis, particularly in the lung, is processes mediated by free radicals generated in CS. This is in agreement with the concept that free-radical mediated oxidative stress is capable of causing tissue damage and disease states, and oxidative damage is strongly suspected to initiate carcinogenesis.

Oxidative stress has been defined by Helmut Sies as a condition in which "a disturbance of the pro-oxidant/anti-oxidant balance occurs in favor of the former leading to biological damage." Indeed numerous studies indicate that cigarette smoking is associated with increased oxidant generation and antioxidant depletion tipping the oxidant/antioxidant balance toward the oxidant side and producing oxidative stress.[18]

MECHANISMS OF INJURY FROM CIGARETTE SMOKING

The lungs, due to their high blood supply and large surface area, are constantly in a high-oxygen environment. In addition, the lung epithelium is also constantly exposed to oxidants generated endogenously during respiration from mitochondrial electron transport, from activated inflammatory cells that influx into the lungs and exogenously from CS and air pollutants, such as ozone, nitrogen dioxide, and combustion particulates, as a result of its exposure to the environment. When the resident antioxidants are insufficient or fail to unregulate sufficiently to neutralize an increased oxidant burden oxidative stress occurs.

ROS, either non-radical, such as H_2O_2 or oxygen radicals, such as O_2^- and the OH that are highly unstable species with unpaired electrons are capable of initiating oxidation, and together with reactive nitrogen species result in a variety of adverse consequences ranging from cell necrosis, senescence, apoptosis, autophagy, lipid peroxidation and protein carbonylation, inflammatory responses, epigenetic changes, remodeling of extracellular matrix and blood vessels, endothelial dysfunction, inactivation of antiproteases, mucus hypersecretion, and impaired tissue repair.

Chronic obstructive pulmonary disease (COPD) is also a disease-associated with aging, which has been shown to result in a decline in the endogenous antioxidant defenses resulting in less protection against oxidative stress. All of these processes are intimately associated with oxidative stress.[19] It is known that CS results in oxidative stress, an imbalance between oxidants and antioxidants in favor of oxidants, and that it activates the vascular endothelium.[20] The activated endothelium favors inflammation, a hallmark feature of COPD. Several studies describe an increase in macrophages, monocytes that have migrated from the vascular space into alveolar space, in the lungs of smokers and individuals with COPD.[21] Macrophages produce ROS that cause oxidative stress leading to apoptosis, senescence, and inflammation-all of which have been described in the airways of smokers with COPD.[22,23] Ultimately, CS affects the lung leading to oxidative stress, inflammation, and disease.

CONCLUSION

In the present review revealed that years of research into the effects of cigarette smoking have led to the conclusion that cigarette smoking represents an important risk factor for so many diseases affecting numerous biological systems in human as well as animals.

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