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Review Article Pathology

FREE REDICAL INJURY AND OXIDATIVE STRESS: A REVIEW

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ABSTRACT Free radical is referred to an atom with a single unpaired electron, within a biological system. Free radicals can react indiscriminately with neighbouring molecules causing extensive cellular damage which is termed as oxidative stress. Oxidative stress can arise for many reasons including consumption of alcohol, medications, trauma, cold, air pollutants, toxins and radiation Air pollutants induced oxidative stress adversely affects health, particularly the pulmonary system.

Ambient air contains a range of pollutants such as nitrogen oxide, ozone and particulate materials. Out of them, ozone derived from photochemical smog, have the ability to drive free radical reactions which gives rise to oxidative stress within the lung. This process initiates responses that are particularly dangerous to susceptible population.

KEYWORDS : Free Radical, oxidative stess , Toxins, Pollutants

Introduction:-

Our bodies have powerful natural systems designed to protect our health. The risk of infectious diseases or cancers increases as our immune system gets weaker and weaker through the ageing and other processes. Every second of our life, our cells are bombarded by particles called free radicals. Normally, they protect us from bacteria viruses and other foreign substances. When our antioxidant defences are adequate, damage caused by those free radicals is repaired without many consequences. However, when excessive amount of free radicals generates, it can damage proteins, lipids, enzymes and DNA that can alter downstream cell signaling and cause a variety of diseases.[1]

Reactive oxygen species (ROS) including the hydroxyl radical, superoxide anion, singlet oxygen, and peroxynitrate, figures prominently in the etiology and progression of numerous cancers. During endogenous metabolic reactions, aerobic cells produce ROS such as superoxide anion (O2•-), hydrogen peroxide (H2O2), hydroxyl radical (OH•), and organic peroxides as normal products of the biological reduction of molecular oxygen. Oxygen radicals are not only generated in the mitochondria, neutrophils and macrophages produce ROS via a plasma membrane bound nicotinamide adenine dinucleotide phosphate, reduced form (NADPH)-oxidase. The radicals are generated for cell killing and bactericidal activities. The NADPH-oxidase is not exclusive to these cells, however, panels of human tumour cell lines were shown to produce large quantities of hydrogen peroxide in vitro. [2]

Most ROS are generated in cells by the mitochondrial respiratory chain. Under normal metabolic conditions, these ROS are eliminat ed rapidly in normal cells by a wide variety of enzymatic and non-enzymatic antioxidant defences. The imbalance between produc tion of reactive oxygen species (ROS) and their elimination by antioxidant defence system results in oxidative stress. Exposure to endogenous and environmental carcinogens causes DNA damage, protein and lipid oxidation indicative of oxidative stress, with consequences for cytotoxic and mutagenic activity as well as aberrant changes to cell cycle progression and replication which potentially impact on the whole organism. Oxygen free radicals are powerful DNA damaging agents that can cause base substitution, deletion, and strand fragmentation which may inactivate tumour suppressor genes within tumour cells or increase expression of proto-oncogenes that are critical initial events in carcinogenesis. Moreover, oxidation of cellular lipids and proteins can adversely affect several steps of the carcinogenic process through changes in a variety of cell regulatory functions, including signal transduction and gene expression. [3]

Trace elements are major components of antioxidant enzymes. A growing body of evidence has indicated that many trace elements play an important role in a number of biological processes by activating or inhibiting enzymes, by competing with other elements and metalloproteins for binding sites or by affecting the permeability of cell membranes. Thus, trace elements may exert action, directly or indirectly, on the carcinogenic process. [4]

Reactive oxygen species (ROS) are involved in a variety of different cellular processes ranging from apoptosis and necrosis to cell proliferation and carcinogenesis. ROS play vital role in the stimulation of signaling pathways in cells in response to changes in intra- and extracellular environmental conditions. ROS can modify many intracellular signaling pathways including protein phosphatases, protein kinases, and transcription factors, suggest ing that the majority of the effects of ROS are through their actions on signaling pathways rather than via non-specific damage of macromolecules.[1]

Three models of free radical-induced cell injury are presented in this review. Each model is described by the mechanism of action of few prototype toxic molecules. Carbon tetrachloride and monobro motrichloromethane were selected as model molecules for alkylating agents that do not induce GSH depletion. Bromobenzene and allyl alcohol were selected as prototypes of GSH depleting agents. Paraquat and menadione were presented as prototypes of redox cycling compounds. All these groups of toxins are converted, during their intracellular metabolism, to active species which can be radical species or electrophilic intermediates. In most cases, the activation is catalyzed by the microsomal mixed function oxidase system, while in other cases (e.g. allyl alcohol) cytosolic enzymes are responsible for the activation.[8]

Radical species can bind covalently to cellular macromolecules and can promote lipid peroxidation in cellular membranes. Of course, both phenomena produce cell damage as in the case of CCl_4 or $BrCCl_3$ intoxication. However, the covalent binding is likely to produce damage at the molecular site where it occurs; lipid peroxidation, on the other hand, besides causing loss of membrane structure, also gives rise to toxic products such as 4-hydroxyalkenals and other aldehydes which in principle can move from the site of origin and produce effects at distant sites.[8]

Electrophilic intermediates readily reacts with cellular nucleophiles, primarily with GSH. The result is a severe GSH depletion as in the case of bromobenzene or allyl alcohol intoxication. When the depletion reaches some threshold values, lipid peroxidation develops abruptly and in an extensive way. This event is

accompanied by cellular death. The reason for which lipid peroxidation develops in a cell severely depleted of GSH remains to be clarified. Probably the loss of the defence systems against a constitutive oxidative stress is not compatible with cellular life.[8]

Some free radicals generated by one-electron reduction can react with oxygen to give superoxide anions which can be converted to other more dangerous reactive oxygen species. This is the case of paraquat and menadione. Damage to cellular macromolecules is due to the direct action of these oxygen radicals and at least in the menadione-induced cytotoxicity, lipid peroxidation is not involved.[8]

All these initial events affect the protein sulfhydryl groups in the membranes. Since some protein thiols are essential components of the molecular arrangement responsible for the Ca2+ transport across cellular membranes, loss of such thiols can affect the calcium sequestration activity of subcellular compartments, that is the capacity of mitochondria and microsomes to regulate the cytosolic calcium level. Altered redistribution of Ca_2+ in cellular compartm ents and in particular a sustained increase in the cytosolic Ca^{2+} level may represent the trigger for the final common pathway leading to cell death.[8]

Cancer is a multistage process defined by at least three stages: initiation, promotion, and progression. Oxidative stress interacts with all three stages of this process. During the initiation stage, ROS may produce DNA damage by introducing gene mutations and structural alterations of the DNA. In the promotion stage, ROS can contribute to abnormal gene expression, blockage of cell- to cell communication and modification of second messenger systems, thus resulting in an increase of cell proliferation or a decrease in apoptosis of the initiated cell population. Finally, oxidative stress may also participate in the progression stage of the cancer process by adding further DNA alterations, lipid peroxidation and protein oxidation to the initiated cell population.[1]

Discussion:-

Free radicals are atoms or molecules that are highly reactive with other cellular structures because they contain unpaired electrons. Free radicals are natural by-products of ongoing biochemical reactions in the body, including ordinary metabolic processes and immune system responses. Free radical-generating substances can be found in the food we eat, the drugs and medicines we take, the air we breathe, and the water we drink. These substances include fried foods, alcohol, tobacco smoke, pesticides, air pollutants, and many more. Free radical can cause damage to parts of cells such as proteins, DNA, and cell membranes by stealing their electrons through a process called oxidation. (This is why free radical damage is also called "oxidative damage.") When free radicals oxidize important components of the cell, those components lose their ability to function normally, and the accumulation of such damage may cause the cell to die. Numerous studies indicate that increased production of free radicals causes or accelerates nerve cell injury and leads to disease.

Antioxidants, also known as "free radical scavengers," are compounds that either reduce the formation of free radicals or react with and neutralize them. Antioxidants often work by donating an electron to the free radical before it can oxidize other cell components. Once the electrons of the free radical are paired, the free radical is stabilized and becomes non-toxic to cells. Therapy aimed at increasing the availability of antioxidants in cells may be effective in preventing or slowing the course of neurological diseases.

Consequences of oxidative stress are: (1) it can increase mutation rate and accelerate tumour progression by inactivating tumour suppressor genes within tumour cells or by increasing expression of proto-oncogenes, (2) it can activate the growth-promoting signaling pathways, (3) Adaptation to oxidative stress results in increased resistance to therapy. Severe oxidative stress leads to apoptosis. Conversely, persistent oxidative stress at sublethal levels may cause resistance to apoptosis, (4) it can increase blood supply to tumour cells. Oxygen radicals increase tumour cell production of the angiogenic factors IL-8 and vascular endothelial growth factor (VEGF).

Extensive investigations over the past decade have uncovered that chronic inflammation can promote all stages of tumorigenesis, including DNA damage, replication, apoptosis, angiogenesis, growth signaling, tissue invasion or metastasis. Chronic inflamm ation is triggered by environmental (extrinsic) factors (eg, infection, tobacco, asbestos) and host mutations (intrinsic) factors (eg, Ras, Myc, p53). However, the precise molecular mechanisms involved and the interconnecting crosstalk between pathways remain incompletely understood. Damage associated molecular patterns (DAMPs) are endogenous molecules released from dying host cells upon oxidative stress or tissue damage can trigger TLR family of receptors involved in alerting the innate immune system of danger [5]. Elevated expression of some TLRs has been reported in many tumor cells, tissues or tumor cell lines which may play a crucial role promoting angiogenesis and metastasis [6]. Toll-like receptor 9 (TLR9) is a cellular DNA-receptor whose activation with cognate ligands triggers an immune reaction, with increased production of inflammatory cytokines, chemokines. Recent publications revealed the existence of a soluble form of TLR9 in human plasma, serum and pleural effusions [7].

Activated inflammatory cells also generate and release large quantities of free radicals which attack local tissue components and cause cell injury. Free radical derived ozonation product breathing results in a range of respiratory symptoms of the healthy population effects include decreased lung function, increased air way hyperactivity and pulmonary inflammation.

Nitrogen dioxide, nitrogen centered free redial, reacts with substrate present in lung lining fluid. Particles less than 10 ppm adversely affect health. Out of them, soluble transitional metals also develop oxidative stress.

Exposure to air pollution in different climatic condition is an important determinant of pulmonary damage. Although each environmental pollutant has its own mechanism of toxicity, most pollutants like ozone, nitrogen oxide, particulate and transition metals are oxidants or capable of reactive oxygen species production which trigger biological process like inflammation and cell death.

Conclusion:-

Short and long-term exposure to air pollution has consistently been to linked to adverse health outcome such as acute respiratory infection specially in children, cancers of respiratory systems and other cardiopulmary disease leading to morbidity, mortality and disability. Awareness should be emphasized among the health workers and health system planners about the public health hazards of air pollutants induced oxidative stress and as well as the remedies to overcome the challenges.

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