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Role of oxidative stress in various diseases: Relevance of dietary antioxidants

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Abstract

Oxidative stress plays important role in the pathophysiology of various diseases. Oxidative stress is caused in body due to an imbalance between the activities of endogenous pro-oxidative enzymes. Cellular antioxidants are known to change their redox state and they can be targeted for destruction, regulate oxidative processes involved signal transduction, effect gene expression and the pathways of cell proliferation and death. Oxidants and antioxidants play an important role in maintaining a balance between free radicals produced by metabolism or derived from environmental sources and the antioxidant system of the body. A natural antioxidant system exists in the biological systems which is responsible for prevention of damage by pro-oxidants. Impaired endogenous antioxidant system results in accumulation of free radicals, which not only induces lipid peroxidation but also imposes severe stress on the body leading to many diseases such as Alzheimer's disease, Parkinson disease, Diabetic neuropathy, various cardiovascular diseases. Antioxidant system may be intrinsic or extrinsic. Intrinsic involves body own neutralizing systems and extrinsic antioxidant involves dietary supplements that are taken in the form of food like vitamin C, vitamin E and beta carotene that can be gained from the fruits and vegetables for the prevention and management of diseases induced by free radicals.

Keywords: Oxidative stress, Free radicals, Anti-oxidants.

Introduction

Oxidative stress is mainly caused by an imbalance between the activity of endogenous pro-oxidation enzymes (such as NADPH oxidase, xanthine oxidase or the mitochondrial dismutase, glutathione peroxidase, heme oxygenase, thio redoxin peroxidase/ peroxiredoin, catalase and paraoxonase). Endogenous reactive intermediates including photoexcited states of tissue chromophores, reactive oxygen species (ROS), reactive carbony species (RCS), transition metal ions and Schiff bases have been implicated in the initiation and progression of diverse human pathologies including tumorgenesis, atheroscelorosis, diabetes and neurodegenerative, disease. Oxidative stress is also implicated in the cognitive deterioration associated with normal aging as well as neurodegenerative disorders such as Alzheimer's and Parkinson's disease.[1] Endothelial cells control vascular homeostasis by generating paracrine factors that regulate vascular tone, inhibit platelet function, prevent adhesion of leukocytes and limit proliferation of vascular smooth muscle. The dominant factor responsible for many of those effects is endothelium derived nitric oxide. Endothelial dysfunction characterized by enhanced inactivation or reduced synthesis of NO, alone or in combination, is seen in conjunction with risk factors for cardiovascular diseases. Endothelial dysfunction can promote vasospasm, thrombosis, vascular inflammation and proliferation of the intima.[1]

Vascular oxidative stress and increased production of reactive oxygen species contributes to mechanisms of vascular dysfunction and has been implicated to play an important role in a number of cardiovascular pathologies, including hypertension, atherosclerosis, myocardial infarction, ischemia/reperfusion injury, and restenosis after angioplasty or venous bypass grafting.[3]

Autoimmune diseases such as type 1 diabetes mellitus (DM1) are believed to result from the failure of immunological tolerance to protein self antigens. It has been proposed that alterations in self antigens could initiate the process of autoimmunity.[4] If the mitochondria are dysfunctional or cells are under stress, such as during high metabolic demand, viral infections, or exposure to certain cytokines/toxins, cells may produce a sufficient amount of radical oxygen or radical nitrogen species (ROS/RNS) to overwhelm the antioxidant systems that normally neutralize these free radicals.[5] A number of oxidative protein modifications have been described in autoimmune diseases.[6] Oxidative modifications produced high molecular weight complexes of glutamic acid decarboxylase (GAD) and sera from type 1 diabetic patients bound these complexes much more strongly than the monomer GAD autoantigen.[7] It has been shown that several of the autoantigens targeted in diffuse scleroderma are uniquely susceptible to cleavage by ROS.[8] Oxidation of beta-2-glycoprotein, a target of antiphospholipid antibodies with

hydrogen peroxide rendered this protein able to activate immature monocyte-derived dendritic cells.[9] It has been shown that the insulin-producing beta cells in the islet of Langerhans are particularly vulnerable to damage by free radicals.[10] Involvement of cytochrome P450 (CYP) enzymes in the pathogenesis of autoimmune hepatitis type 2, occurring via molecular mimicry of human cytochrome P450 by hepatitis C virus at the level of cytotoxic T cell recognition, is well appreciated.[11] In addition, two different cytochrome P450 enzymes are believed to be the adrenal antigens in autoimmune polyendocrine syndrome type I and Addison's disease.[12]

Neurodegenerative disorders are a heterogeneous group of diseases of the nervous system, including the brain, spinal cord, and peripheral nerves that have much different aetiology. Many are hereditary, some are secondary to toxic or metabolic processes, and others result from infections. Due to the prevalence, morbidity, and mortality of the neurodegenerative diseases, they represent significant medical, social, and financial burden on the society. Neuropathologically, these are characterised by abnormalities of relatively specific regions of the brain and specific populations of neurons. The degenerating neuron clusters in the different diseases determine the clinical phenotype of that particular illness. Recent investigations in medical genetics have identified specific genes for various neurodegenerative disorders and specially bred animal models have begun to be used to study the aetiological factors and underlying pathogenic mechanisms. There are three learning objectives of basic neuroscience: (i) understanding of fundamental concepts of neurodegenerative disorders, (ii) recognition of specific morphological (gross and microscopic) features of each major disease and their general correlation to disease manifestations, and (iii) developing an understanding of genetics, treatment options, and clinical features of each individual disease.[13]

Free radicals are highly reactive molecules or chemical species capable of independent existence. Generation of highly reactive oxygen species (ROS) is an integral feature normal cellular function like mitochondrial respiratory chain, phagocytosis, arachidonic acid metabolism, ovulation and fertilization. The production however, multiplies several folds during pathological conditions. The release of oxygen free radicals has also been reported during the recovery phases from many pathological noxious stimuli to the cerebral tissues.[14]

The emerging challenge in understanding the pathogenesis of Parkinson's disease includes abnormalities in cellular protein transport, interaction between proteins and protein aggregation (1). Recent advances in both molecular genetics and neurochemistry have shown involvement of excitotoxicity and oxidative stress in cell death.[15] Parkinson's disease is pathologically characterized by loss of catecholaminergic neurons in the brainstem. Numbers of biochemical processes are involved in pathogenesis and progression of neurological disorders. The concept of oxidative stress and antioxidants may be directly or indirectly involved in the pathogenesis of Parkinson's disease.[16-18]

Alzheimer's disease (AD) is the most common neurodegenerative disease that causes dementia in the elderly. It is characterized by the gradual deterioration of memory and other cognitive functions, which eventually leads to a complete incapacity and death of the patients within 3 to 9 years after diagnosis.[19] The major pathological characteristics of AD brains are the presence of senile plaques, neurofibrillary tangles (NFTs), and neuronal loss.[20]

Senile plaques are mainly composed of beta-amyloid peptide that is produced from proteolytic cleavage of the transmembrane amyloid precursor protein (APP). NFTs are formed by arrays of paired helical filaments (PHFs) structures, which contain mainly self-aggregated hyperphosphorylated tau, a multifunctional protein involved in microtubule assembly and stabilization.[20]

Diabetic neuropathy (DN), a micro vascular complication of diabetes, comprises disorders of peripheral nerve in people with diabetes when other causes are ruled out. Diabetic peripheral neuropathy (DPN) is associated with considerable mortality, morbidity, and diminished quality of life.[21] The prevalence of neuropathy in diabetic patients is about 30%, whereas up to 50% of patients will certainly develop neuropathy during their disease.[22]

What is oxidative stress?

Oxidative stress is mainly caused by an imbalance between the activity of endogenous pro-oxidation enzymes (such as NADPH oxidase, xanthine oxidase or the mitochondrial dismutase, glutathione peroxidase, heme oxygenase, thio redoxin peroxidase/ peroxiredoin, catalase and paraoxonase). Endogenous reactive intermediates including photoexcited states of tissue chromophores, reactive oxygen species (ROS), reactive carbony species (RCS), transition metal ions and Schiff bases have been implicated in the initiation and progression of diverse human pathologies including tumogenesis, atherosclerosis, diabetes and neurodegenerative, disease. Oxidative stress is also implicated in the cognitive deterioration associated with normal aging as well as neurodegenerative disorders such as Alzheimer's and parkinson's disease.[1] Endothelial cells control vascular homeostasis by generating paracrine factors that regulate vascular tone, inhibit platelet function, prevent adhesion of leukocytes and limit proliferation of vascular smooth muscle. The dominant factor responsible for many of those effects is endothelium derived nitric oxide. Endothelial dysfunction characterized by enhanced inactivation or reduced synthesis of NO, alone or in combination, is seen in conjunction with risk factors for cardiovascular diseases. Endothelial dysfunction can promote vasospasm, thrombosis, vascular inflammation and proliferation of the intima.[2]

Role of oxidative stress in cardiovascular system diseases

Endothelial cells control vascular homeostasis by generating paracrine factors that regulate vascular tone, inhibit platelet function, prevent adhesion of leukocytes and limit proliferation of vascular smooth muscle. The dominant factor responsible for many of those effects is endothelium derived nitric oxide. Endothelial dysfunction characterized by enhanced inactivation or reduced synthesis of NO, alone or in combination, is seen in conjunction with risk factors for cardiovascular diseases. Endothelial dysfunction can promote vasospasm, thrombosis, vascular inflammation and proliferation of the intima.[2]

Oxidative stress has been identified as critical in most of the key steps in the pathophysiology of atherosclerosis and acute thrombotic events, including dyslipidemia leading to atheroma formation, the oxidation of LDL, endothelial dysfunction, plaque rupture, myocardial ischemic injury, and recurrent thrombosis (i.e., the secondary or subsequent clot that often occurs after initial thrombolysis). The role of oxidative stress in the connection between the various coronary disease risk factors such as elevated blood pressure, diabetes and cigarette smoking, and the clinical sequelae of disease associated with vasoconstriction, thrombosis, plaque rupture, and vascular remodelling has been recognized.[23]

Oxidative stress is an important mediator of both abnormal platelet function and dysfunctional endothelium-dependent vasodilation in the setting of cardiovascular disease. Superoxide anion is an important source of oxidative stress, has direct effects, and limits the biological activity of NO. Excessive vascular superoxide production drives further platelet activation and recruitment leading to greater thrombus formation. The occurrence of superficial intimal injury caused by endothelial denudation and deep intimal injury caused by plaque rupture expose collagen and Tissue Factor (TF) to platelets. Local platelet activation stimulates further thrombus formation and additional platelet recruitment by supporting cell-surface thrombin formation and releasing potent platelet agonists such as adenosine diphosphate (ADP), serotonin, and thromboxane A2. A thrombus forms as platelets aggregate via the binding of bivalent fibrinogen to GP IIb/IIIa. Platelet NO release influences platelet recruitment to the growing thrombus and impaired platelet-derived NO release is likely

associated with acute coronary and stroke syndromes. Antioxidants may indirectly inhibit platelets through scavenging of reactive oxygen species, many of which alter platelet function. Despite the different sub cellular locations of water- and lipid-soluble antioxidants, these antioxidant pathways in platelets are closely linked. Antioxidants may also indirectly inhibit platelets through the metabolism of reactive oxygen species, many of which alter platelet function. Inflammation is linked with the evolution of cardiovascular disease and acute coronary syndromes.[24]

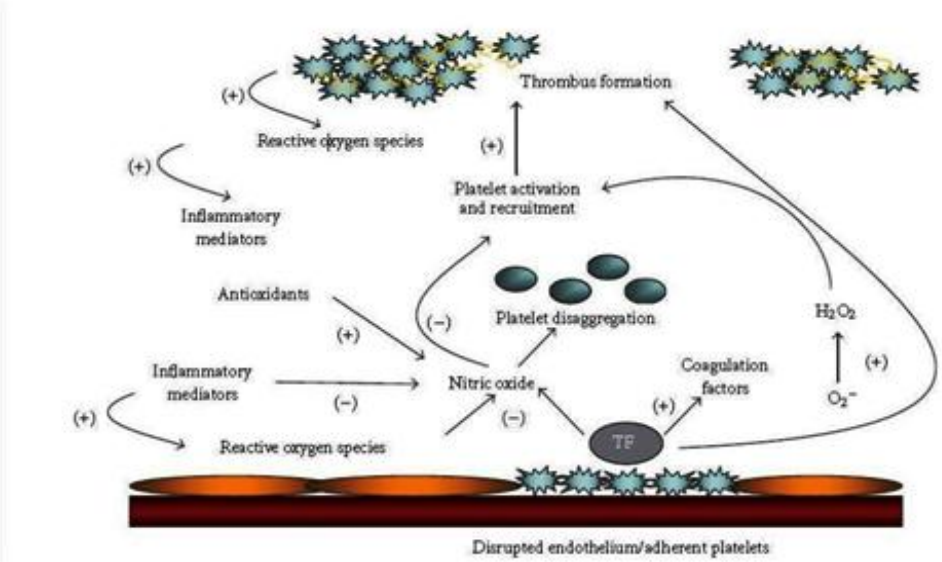

Figure 1: Oxidative stress mediates abnormal platelet function and dysfunctional endothelium-dependent vasodilation.

Oxidative stress in neurodegenerative diseases

Damage caused due to free radicals caused by ROS leads to several damaging effects as they can attack lipids, protein, enzymes, carbohydrates, and DNA in cells and tissues. They induce undesirable oxidation, causing membrane damage, protein modification, DNA damage, and cell death induced by DNA fragmentation and lipid peroxidation. This oxidative damage/stress, associated with ROS is believed to be involved not only in the toxicity of xenobiotics but also in the pathophysiological role in aging of skin and several diseases like heart disease (atherosclerosis), cataract, cognitive dysfunction, cancer (neoplastic diseases), diabetic retinopathy, critical illness such as sepsis and adult/acute respiratory distress syndrome, shock, chronic inflammatory diseases of the gastrointestinal tract, organ dysfunction, disseminated intravascular coagulation, deep injuries, respiratory burst inactivation of the phagocytic cells of immune system, production of nitric oxide by the vascular endothelium, vascular damage caused by ischaemia reperfusion known as ischaemia/reperfusion injury and, release of iron and copper ions from metalloprotein.[25] Iron changes have been detected in multiple sclerosis, spastic paraplegia, and amyotrophic lateral sclerosis, which reinforces the belief that iron accumulation is a secondary change associated with neurodegeneration in these diseases, although it could also be related to gliosis (glia might produce free radicals) in the diseased area, or the changes in the integrity of the blood brain barrier caused by altered vascularisation of tissue or by inflammatory events.[26] Characteristic features of some neurodegenerative diseases are shown in table 1.[27]

Table 1: Characteristic features of some neurodegenerative diseases

Neurodegenerative Diseases	**Clinical Feature**	**Neuropathology**
Alzheimer's disease (AD)	Dementia, progressive deterioration of thought, judgement, language skills, visual-spatial perception and mood	Generalized cortical atrophy with shrinkage of the amygdala and hippocampus. Selective dysfunction and death of neocortex, hippocampus, amygdale, basal forebrain and brainstem. The senile plaque an extracellular deposit of amyloid composed of Ab peptide derived from amyloid precursor protein
Amyotrophic Lateral Sclerosis (ALS)	Progressive weakness and atrophy of skeletal muscles. Weakness of chest muscles and diaphragm, muscles dysfunction in the pharynx and larynx lead to respiratory problems and death with bronchopneumonia.	End stage disease is characterised by loss of primary motor neurons in neocortex. Motor neurons have abnormal phosphorylated neurofilaments.
Huntigton's disease (HD)	HD patients develop cognitive impairments (dementia), personality changes and variety of psychological symptoms including irritability, depression and eventually become mute	Marked atrophy of the striatum (caudate and putamen) and generalized cortical atrophy with decreased brain weight. Neurons have been shown to have intranuclear inclusions with cleaved fragments of mutant Huntigton with expanded triplet repeat.
Parkinson disease (PD)	Slowness of voluntary movements (bradykinesia), rigidity, tremor, cognitive deficits (dementia) i.e. post encephalitic parkinsonism. A mitochondrial toxin called MPTP induces parkinsonism.	Neuronal degeneration due to loss of pigmented neurons in substantia nigra (pars compacta). The toxic metabolite MPP^+ derived from MPTP inhibits the mitochondrial complex I leading to ATP depletion and generation of toxic oxygen free radicals.

Oxidative stress in Parkinson disease

Parkinson's disease (PD) is considered one of the major neurological disorders of the population over 65 years of age and about 3% of the population over the age of 65 have PD. There are convincing evidences that the oxidative stress and reactive oxygen species (ROS) play an important role in the aetiology and/or progression of a number of human diseases.[28] Parkinson disease is a progressive neurodegenerative disorder affecting primarily the dopamine neurons that arise in the midbrain and project to the putamen and caudate regions (the striatum) of the brain, areas concerned with the control of motor movements.[29]

The metabolism of dopamine by action of enzyme monoamine oxidase is accelerated in Parkinson's disease and excessive formation of hydrogen peroxide (H_2O_2) takes place. In subsequent reactions H_2O_2 hydroxyl radicals are generated. As per reports, the activity of monoamine oxidase is increased in Parkinson's disease.[30] This increased activity of monoamine oxidase may further metabolize dopamine to produce excessive formation of hydrogen peroxide. The polymerization of auto-oxidative products of dopamine may lead to the formation of characteristic pigmentation of the substantia nigra. These released free radicals might be responsible for the loss of dopaminergic neurons.[31, 32]

Oxidative stress in Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disease that causes dementia in the elderly. It is characterized by the gradual deterioration of memory and other cognitive functions, which eventually leads to a complete incapacity and death of the patients within 3 to 9 years after diagnosis.[19] The major pathological characteristics of AD brains are the presence of senile plaques, neurofibrillary tangles (NFTs), and neuronal loss.[20]

There are various hypothesis proposed in support of induction of AD pathogenesis, wherein oxidative stress has emerged as one of the factors in AD pathogenesis, the mechanism by which redox balance is altered and sources of free radicals remain elusive. According to a hypothesis linkage between oxidative stress and Abeta-induced toxicity has been considered. In various AD transgenic mouse models carrying mutants of APP and PS-1, increased hydrogen peroxide and nitric oxide production as well as elevated oxidative modifications of proteins and lipids were correlated with the age associated Abeta accumulation, confirming that Abeta promotes oxidative stress.[33–37] In hippocampal neuronal cell cultures, the induction of reactive oxygen species (ROS) by soluble Abeta oligomers required the activation of N-methyl- D-aspartate (NMDA) receptor and was associated with a rapid increase in neuronal calcium levels, suggesting a possible role of soluble Abeta oligomers as proximal neurotoxins and the involvement of oxidative stress in the synaptic impairment and neuronal loss induced by soluble Abeta oligomers.[38]

According to another hypothesis which involves mitochondria dysfunction extensive studies have demonstrated that mitochondria dysfunction is an important factor involved in the pathogenesis of AD. A number of mitochondrial and metabolic abnormalities have been identified in the hippocampal neurons of AD compared to age-matched controls.[39–41] Morphometric analysis of biopsies from AD brains showed a significant reduction of mitochondria, while the mitochondrial DNA and protein were increased in the cytoplasm and in the vacuoles associated with lipofuscin, a lysosome suggested as the site of mitochondrial degradation by autophagy.[39-41] These mitochondrial abnormalities were found accompanied by oxidative damage marked by 8-hydroxyguanosine and nitrotyrosine, indicating that the mitochondria were damaged during the progression of AD.[39]

On a third front linkage between the homeostasis of metals present in body and oxidative stress is discussed Transition metals such as copper (Cu), zinc (Zn), and iron (Fe) play important catalytic roles in many enzymes and are essential for a broad range of biological processes in human body including brain functions. Both Cu and Zn have been shown to participate in regulating synaptic function. Following NMDA receptor activation, Cu is released from the neuron and regulates neuronal activation by functionally blocking NMDA receptors and limiting calcium entry into the cell.[42] Zn also has a neuromodulatory role; it is released from presynaptic nerve terminals into the synaptic cleft upon neuronal activation and has been shown to inhibit excitatory NMDA receptors.[43] Fe is crucial for neuronal processes such as myelination, synaptogenesis, and synaptic plasticity (SP). It is well documented that deficiency of Fe can induce a series of neurochemical alterations that may eventually lead to cognitive deficits.[44] While these transition metals play essential roles in neural functions, their levels and transport are strictly regulated, as aberrant metal homeostasis can result in neurotoxic free-radical production. For example, excess Fe or Cu can directly interact with oxygen to produce superoxide ion, hydrogen peroxide, and hydroxyl radical, which may lead to oxidative stress and a cascade of biochemical alterations that eventually cause neuronal cell death.[45] In fact, growing evidence has shown that there is a close relationship between the disruption of metal homeostasis and AD.[45] Abnormal levels of Cu, Zn, and Fe have been observed in AD hippocampus and amygdala, areas showing severe histopathologic alterations.[46] Moreover, these transition metals have been detected within the amyloid deposits in AD patients as well as transgenic mouse models.[47–49]

Antioxidants and role of food products as antioxidants

Antioxidants are the species that compensate the effect of oxidants or they are the compounds that act against the ROS and hence prevent the loss to be made of the body. They are two types of antioxidants systems *(i) Endogenous antioxidants:* Biological systems have evolved with endogenous defence mechanisms to help protect against free radical induced cell damage. Glutathione peroxidase, catalase, and superoxide dismutases are antioxidant enzymes, which metabolize toxic oxidative intermediates. They require micronutrient as cofactors such as selenium, iron, copper, zinc, and manganese for optimum catalytic activity and effective antioxidant defence mechanisms.[50-51] SOD, catalase, and glutathione peroxidase are three primary enzymes, involved in direct elimination of active oxygen species (hydroxyl radical, superoxide radical, hydrogen peroxide) whereas glutathione reductase, glucose-6-phosphate dehydrogenase, and cytosolic GST are secondary enzymes, which help in the detoxification of ROS by decreasing peroxide levels or maintaining a steady supply of metabolic intermediates like glutathione and NADPH necessary for optimum functioning of the primary antioxidant enzymes.[52-53] Glutathione, ascorbic acid, alpha-tocopherol, betacarotene, bilirubin, selenium, NADPH, butylhydroxyanisole (BHA), mannitol, benzoate, histidine peptide, the iron-bonding transferrin, dihydrolipoic acid, reduced CoQ10, melatonin, uric acid, and plasma protein thiol, etc., as a whole play a homoeostatic or protective role against ROS produced during normal cellular metabolism and after active oxidation insult. Glutathione is the most significant component which directly quenches ROS such as lipid peroxides and plays major role in xenobiotic metabolism. When an individual is exposed to high levels of xenobiotics, more glutathione is utilised for conjugation making it less available to serve as an antioxidant. It also maintains ascorbate (vitamin C) and alpha-tocopherol (vitamin E), in their reduced form, which also exert an antioxidant effect by quenching free radicals.[54-56]

(ii) Exogenous antioxidants: Contribution from diet.

The most widely studied dietary antioxidants are vitamin C, vitamin E, and beta-carotene. Vitamin C is considered the most important water-soluble antioxidant in extracellular fluids, as it is capable of neutralising ROS in the aqueous phase before lipid peroxidation is initiated. Vitamin E is a major lipid-soluble antioxidant, and is the most effective chain-breaking antioxidant within the cell membrane where it protects membrane fatty acids from lipid peroxidation. Beta-carotene and other carotenoids also provide antioxidant protection to lipid rich tissues. Fruits and vegetables are major sources of vitamin C and carotenoids, while whole grains, i.e., cereals and high quality

vegetable oils are major sources of vitamin E.[57-58] A number of other dietary antioxidants exist beyond the traditional vitamins collectively known as phytonutrients or phytochemicals which are being increasingly appreciated for their antioxidant activity, one example is flavonoids which are a group of polyphenolic compounds. These are widely found in plants as glucosylated derivatives. They are responsible for the different brilliant shades such as blue, scarlet, and orange. They are found in leaves, flowers, fruits, seeds, nuts, grains, spices, different medicinal plants, and beverages such as wine, tea, and beer.[59-62] Flavonoids exhibit several biological effects such as antitumoural, anti-ischaemic, anti-allergic, anti-hepatotoxic, antiulcerative, and anti-inflammatory activities. These are also known to inhibit the activities of several enzymes, including lipoxygenase, cyclooxygenase, monooxygenase, xanthine oxidase, glutathione-S-transferase, mitochondrial succino-oxidase, and NADH oxidase, phospholipase A2, and protein kinases. Many of the biological activities of flavonoids are attributed to their antioxidant properties and free radical scavenging capabilities. The antioxidant activities of flavonoids vary considerably depending upon the different backbone structures and functional groups. A number of flavonoids efficiently chelate trace metals, which play an important role in oxygen metabolism. Free iron is a potential enhancer of ROS formation as it leads to reduction of H_2O_2 and generation of the highly aggressive hydroxyl radical. Free copper mediates LDL oxidation and contributes to oxidative damage due to lipid peroxidation.[63-64] Due to the inefficiency of our endogenous defence systems as well as the existence of some physiopathological situations, such as, cigarette smoke, air pollutants, UV radiation, inflammation, ischaemia/reperfusion, etc., ROS can be produced in excess, and increasing amounts of dietary antioxidants will be needed for diminishing the cumulative effect of oxidative damage over an individual's life span.[65]

Conclusion

Free radicals or the reactive oxygen species are accepted into the biochemical and medical orthodoxy. Importance and existence of ROS in living system was ignored.[66] Various studies and regress research came out with the points that oxidative stress has critical role in the pathophysiology of atherosclerosis and acute thrombic events; also it has been implicated in diabetic cardiomyopathy[67, 68] and hypertensive heart disease.[69]

Parkinson disease is the second most common neurodegenerative disorders. Equally strong evidence has implicated oxidative stress in the pathogenesis of Parkinson disease. Brain requires high metal ion concentrations to maintain its functions. Brain has poor capacity to get through with the oxidative stress and demonstrates little regenerative capacity because relative to its size, the brain experiences an increased rate of oxidative activity which creates a significant number of free radicals also brain nerve tissue contain relatively low level of antioxidants. Secondly the brain regions that are rich in catecholamines are exceptionally vulnerable to free radical generation.[70]

Excessive ROS may be generated from mitochondria dysfunction and/or aberrant accumulation of transition metals, perhaps caused by a combination and tau pathology, eventually resulting in oxidative stress. Oxidative stress, which mediates the neurotoxicity, induced by abnormal accumulation of Abeta and tau proteins, may augment Abeta production and aggregation as well as facilitate tau phosphorylation and polymerization, further enhancing a variety of neurotoxic events including ROS production, thus forming a vicious cycle that promotes the initiation and progression of AD. Regardless a primary or secondary event, oxidative stress is an important factor contributing to the development of AD.[71]

Diabetes can cause injury to peripheral nerves in various distributions, which lead to substantial pain, morbidity, and impaired quality of life. Social and health-care costs linked with Diabetic neuropathy (DN) are high. DN develops on a background of hyperglycemia and associated with metabolic imbalance. Numerous biochemical mechanisms of neurovascular and nerve damage have been identified in DN, but excessive production of ROS or oxidative stress is thought to be a common etiologic factor.[72]

The evidence to date for oxidative stress in various neurodegenerative diseases is strongly persuasive. Clinical studies show that a number of events associated with Alzheimer's are capable of stimulating production of free radicals and depletion of antioxidant levels. Patients with Parkinson's also have reduced glutathione levels and free radical damage is found in the form of increased lipid peroxidation and oxidation of DNA bases.[27] Antioxidants have a very good control over the oxidative stress. Therefore, dietary antioxidants should be administered in adequate amount.

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