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History of Tuberculosis

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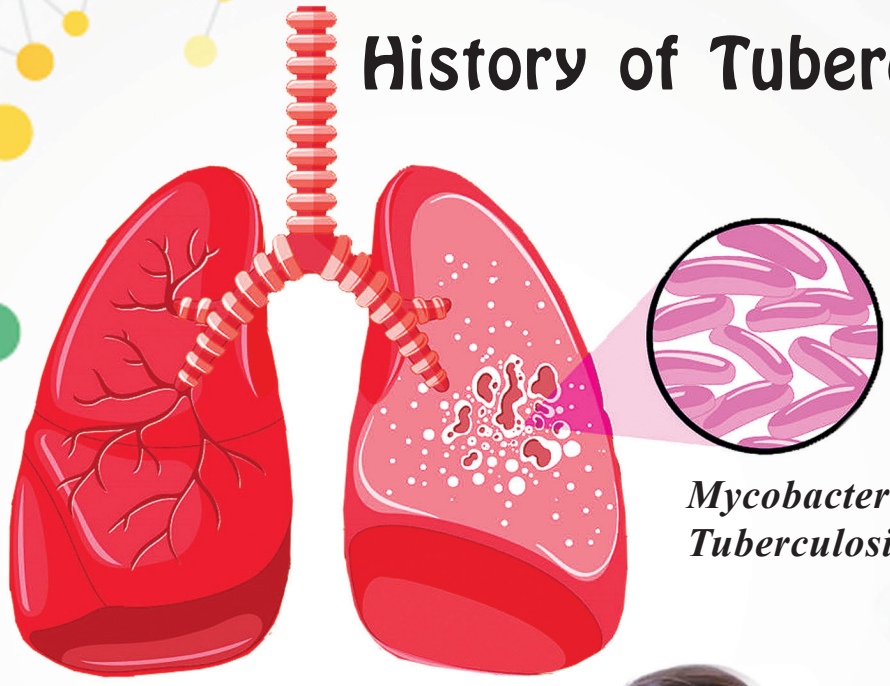

Mycobacterium Tuberculosis

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GENERAL

Antioxidants and Epilepsy

SANJAY AGRAWAL

Introduction

Oxidative stress (OS) is the condition that occurs when the steady-state balance of prooxidants to antioxidants is shifted in the direction of the former, creating the potential for organic damage. Prooxidants are by definition free radicals, atoms, or clusters of atoms with a single unpaired electron[1]. Initially, oxidative stress was described as an imbalance between generation and elimination of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These reactive species were originally considered to be exclusively detrimental to cells, but now it is considered that redox regulation involving ROS is essential for the modulation of critical cellular functions (mainly in astrocytes and microglia), such as mitogene-activated protein (MAP) kinase cascaden activation, ion transport, calcium mobilization, and apoptosis program activation[2].

Oxidative stress has been shown to be associated with alterations in ROS, RNS, and nitric oxide (NO) signaling pathways, whereby bioavailable NO is decreased and ROS and RNS production are increased[3]. Oxidative and nitrosative stress pathways are induced by inflammatory responses, and subsequent mitochondrial metabolic processes generate highly reactive free radical molecules. Indeed, ROS and RNS consist of active moieties that can react with other substrates. Examples of ROS and RNS are superoxide anion, hydroxyl radical, and peroxynitrite. Under physiological conditions defense pathways counterbalance ROS and RNS production, thus in these conditions reactive species have physiological roles that include signaling. In conditions of excessive production or if body defenses are compromised, ROS and RNS may react with fatty acids, proteins, and DNA, thereby causing damage to these substrates[4].

Neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, are defined by progressive loss of specific neuronal cell populations and are associated with protein aggregates. A common feature of these diseases is extensive evidence of oxidative and nitrosative stress (O&NS), which might be responsible for the dysfunction or death of neuronal cells which contributes to pathogenesis[4,5]. These neurodegenerative diseases affect distinct population groups: children, young adults, and the elderly. These diseases are much more prevalent in the elderly as a result of aging, environmental factors and to lesser extent genetic factors[6].

Age, in turn, is an independent risk factor both for neurodegenerative diseases and for epilepsy[7,8]. Epilepsy occurs in about 1%of patients aged over 65 years (about one quarter of newly diagnosed epilepsies)[8–13]. In this population, poststroke epilepsy is predominant, but tumor-associated, traumatic and neurodegenerative pathologies are also commonly associated with epilepsy[8]. in some conditions such as stroke, trauma, or a tumor, the association with the onset of epilepsy may be immediately apparent. However, with insidious neurodegeneration with no clear markers of disease, the link with epilepsy may be less obvious. Thus, given the fact that (i) old age is an important risk factor for epilepsy and neurodegenerative disorders, (ii) neurodegenerative disorders are risk factors for epilepsy, and (iii) O&NS are related to both pathological conditions (epilepsy and neurodegenerative disorders), we decided to conduct a literature review of studies regarding O&NS and age as risk factors for epilepsy and also discuss the role of O&NS pathways in seizure induction and propagation.

Epilepsy

Epilepsy is one of the most common and serious brain disorders in the world. It affects at least 50 million people worldwide. Approximately 100 million people will have at least one epileptic seizure during their lifetime. It causes serious physical, psychological, social, and economic consequences. The median prevalence of lifetime epilepsy for developed countries is 5.8 per 1,000 and 10.3 per 1,000 for developing countries.

Epilepsy: Classification and Etiology

Epilepsy can be classified as idiopathic, provoked or symptomatic. Symptomatic epilepsies may have several causes (trauma, tumor, infection, malformation or a systemic genetic disease); provoked seizures are predominantly caused by specific environmental or

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systemic factors and there are no significant neuroanatomical or neuropathological anomalies. Idiopathic epilepsy is defined as having a predominantly or presumably genetic cause and there are no significant neuroanatomical or neuropathological anomalies. From neuroimaging techniques (computed tomography and magnetic resonance imaging) it is possible to identify the possible structure or anatomy associated with epilepsy, such as tumors, hydrocephalus, congenital lesions, vascular accidents, hippocampal sclerosis. Progress in the field of genetics, with techniques such as the development of sequencing methods, karyotype analysis and DNA amplification methods, has produced the identification of several genes and genetic conditions which include epilepsy in their phenotype. With progress in neuropharmacological studies it is possible to identify Recently Waldbaum et al. investigated whether acute lesions induced by ROS formation contribute mechanically to the formation of chronic epilepsy. They have questioned whether mitochondrial and cellular alterations might occur during the "latency period" between the initial brain lesion and the appearance of recurring spontaneous seizures, inducing progression to chronic epilepsy. An adaptive increase of mtDNA repair occurs immediately after ROS increase induced by acute SE. However, chronic increase in ROS production is accompanied by failure in the induction of mtDNA repair. Although mitochondrial production of H2O2 returns to control levels during the "latency period," measurements of more sensitive OS indexes suggest the occurrence of ongoing OS, especially in the mitochondrial compartment during the "latency period". Oxidative stress (GSH) markers and specific markers of redox status in the mitochondrion (coenzyme A) have recently been demonstrated to decrease in the hippocampus after lithiumpilocarpine induced SE and to become permanently damaged during epileptogenesis and chronic epilepsy, even when H2O2 production measurements and mtDNA damage return to control levels. This may contribute to significant mitochondrial dysfunction, harming neuronal excitability through ETC dysfunction and decreased ATP production. Damage to mtDNA and abnormal mitochondrial H2O2 production has been observed in the hippocampus of rats three months after SE. Such data suggest there is evidence to support the involvement of mitochondrial OS in epilepsy and also suggest that mitochondrial lesions might contribute to epileptogenesis. Such evidence raises an intriguing possibility that mitochondrial dysfunction caused by the production of free radicals may increase susceptibility to seizures.

Epilepsy and Antioxidants

Induced seizures may be partially prevented with treatment using antioxidant substances, such as SOD mimetics, melatonin e vitamin C. Kong et al. have investigated the role of RNA oxidation in epileptogenesis. Using pilocarpine to induce SE, they observed a significant increase in RNA oxidation in vulnerable neurons in rat brains immediately after SE followed by neuronal death. However, a daily supplement of antioxidants (coenzyme Q10) significantly reduced RNA oxidation and protected rats from SE and neuronal loss. These results suggest that RNA oxidation may be an important factor that contributes to the degeneration process in seizures induced by neuron and epileptogenesis. Catalytic antioxidants have been shown to reduce oxidative damage in animals with epilepsy, although they have been unable to reduce the seizure's duration or latency. Pretreatment with EUK 134 (a synthetic superoxide dismutase/ catalase mimetic) prevents neuronal damage and decreases levels of markers of oxidative damage, including protein nitration, resulting from KA-induced seizures. However, EUK-134 does not affect seizure latency or duration.

Sudha et al. studied parameters of oxidative stress (lipid peroxidation, superoxide dismutase (SOD), glutathione peroxidase (GP), glutathione reductase (GR) and catalase), and levels of antioxidant substances (vitamin C, vitamin E, vitamin A, and ceruloplasmin activities) were determined in epileptic patients and normal controls. Patients who were treated with phenobarbital and who did not suffer convulsions for one year were considered for followup. Lipid peroxidation in patients with epilepsy was significantly higher when compared to controls. Moreover, plasma ceruloplasmin concentrations were also markedly increased in these cases. Plasma vitamin C and A concentrations were significantly lower in epileptics when compared to controls. In the follow-up patients, GR levels were significantly higher than in their pretreated condition. Furthermore, plasma vitamin A, E, and C concentrations remained within normal ranges. The results indicate that antioxidant status in the blood of epileptic patients, which was low compared to controls, improved after treatment with AED, suggesting that free radicals may be implicated in epilepsy.

Epidemiological studies showed that increased circulating levels of lipoprotein-associated phospholipase A2 predict an increased risk of stroke. Previous studies showed the importance of lipid peroxidation in the pathogenesis of AD. There is evidence of increased levels of lipid peroxidation and neurotoxic byproducts of lipid peroxidation (HNE) in vulnerable regions of the Alzheimer's disease (AD) brain and increased levels of HNE in the brain tissue from patients affected by mild cognitive disorder and early AD.

Oxidative and nitrosative stress has an important effect on onset and maintenance of seizures, as previously discussed. However, this effect seems to have different impacts on groups of different ages (children, young adults, and the elderly). We know that seizures are more prevalent in old age than in children. This may be due to an increased excitability of primary hippocampal neurons seen with age. The CNS is highly sensitive to oxidative stress, especially in elderly patients. This implies that the elderly have a higher risk of neural diseases such as epilepsy. However, future experimental studies need to confirm the relationship between oxidative stress, the elderly, and epilepsy.

Conclusion

Oxidative stress and mitochondrial dysfunction are involved in neuronal death and seizures. There is evidence that suggests that antioxidant therapy may reduce lesions induced by oxidative free radicals in some animal seizure models. Recent studies have shown that an association between mitochondrial dysfunction and chronic oxidative stress may play an important role in epileptogenesis. However, further preclinical and clinical studies are required to further investigate the relationship between oxidative stress, seizures, and age.

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Oesophageal webs are thin membranous structures which can be congenital or acquired. They are more common in women and involve the cervical oesophagus. Although pathogenesis is unclear, they are associated with iron deficiency bullous skin disorders, and immunological disorders. Plummer Vinson syndrome is a triad of dysphagia, iron deficiency anaemia, and oesophageal webs. It is a precancerous condition associated with an increased risk of upper aerodigestive cancers. Cancer can develop several years after the onset of dysphagia, and the lifetime incidence of cancer in Plummer Vinson Syndrome is reported to be 3-15%.

The risk of cancer in Plummer Vinson Syndrome is higher than in achalasia cardia.

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