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Review Article

Oxidative Stress and Epilepsy: Literature Review

Carlos Clayton Torres Aguiar,[1] Anália Barbosa Almeida,[2] Paulo Victor Pontes Araújo,[2] Rita Neuma Dantas Cavalcante de Abreu,[3] Edna Maria Camelo Chaves,[2] Otoni Cardoso do Vale,[2] Danielle Silveira Macêdo,[2] David John Woods,[4] Marta Maria de França Fonteles,[2,5] and Silvania Maria Mendes Vasconcelos[2]

[1] *School of Medicine, University of Fortaleza (UNIFOR)/RENORBIO, Rua Desembargador Floriano Benevides Magalhães, 221 3° Andar, 60811-690 Fortaleza, CE, Brazil*
[2] *Department of Physiology and Pharmacology, Faculty of Medicine, Federal University of Ceará, Rua Coronel Nunes de Melo, 1127, 60430-270 Fortaleza, CE, Brazil*
[3] *School of Nursing, University of Fortaleza (UNIFOR)/RENORBIO, Avenida Washington Soares, 1321, 60811-905 Fortaleza, CE, Brazil*
[4] *School of Pharmacy, University of Otago, P.O. Box 913, Dunedin, New Zealand*
[5] *Pharmacy Department, Faculty of Dentistry, Nursing and Pharmacy, Federal University of Ceará, Rua Capitão Francisco Pedro, 1210, 60430-370 Fortaleza, CE, Brazil*

Correspondence should be addressed to Silvania Maria Mendes Vasconcelos, silvania_vasconcelos@yahoo.com.br

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Backgrounds. The production of free radicals has a role in the regulation of biological function, cellular damage, and the pathogenesis of central nervous system conditions. Epilepsy is a highly prevalent serious brain disorder, and oxidative stress is regarded as a possible mechanism involved in epileptogenesis. Experimental studies suggest that oxidative stress is a contributing factor to the onset and evolution of epilepsy. *Objective*. A review was conducted to investigate the link between oxidative stress and seizures, and oxidative stress and age as risk factors for epilepsy. The role of oxidative stress in seizure induction and propagation is also discussed. *Results/Conclusions*. 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. Studies have demonstrated that mitochondrial dysfunction is associated with chronic oxidative stress and may have an essential role in the epileptogenesis process; however, few studies have shown an established link between oxidative stress, seizures, and age.

1. 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 cascade 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 disease 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 a 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. [8–14]. 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.

2. Oxidative and Nitrosative Stress

Oxidative stress is defined as an imbalance between oxidants (free radicals); nitrosative stress (NS) refers to processes in which the fluxes of NO become high enough to result in nitrosation of amines and thiols and antioxidants which results in a relative or actual excess of oxidative species and this leads to disruption in signaling, redox control, and/or molecular damage [15]. Free radicals consist of chemical structures which contain one or more unpaired electrons in their outer layer. This property is associated with a highly reactive state and a propensity for chemical reactions. In 1956, Harman proposed the "free radical theory" of the ageing process. He suggested that free radicals produced during aerobic respiration had damaging effects on cell components and connective tissues, causing cumulative damage which results in the process of ageing and eventually death. He initially speculated that free radicals were probably produced by reactions involving molecular oxygen and catalyzed in cells by oxidative enzymes [16]. In 1972, Harman included the involvement of mitochondria in physiological ageing processes. Approximately 90% of all oxygen in a cell is consumed in the mitochondrion, especially in the inner membrane where oxidative phosphorylation occurs [17]. Oxygen is involved in the oxidation of organic compounds and the production of energy for cell metabolism. However, only a very small amount of consumed oxygen (between 2 and 5%) is reduced, which leaves a variety of highly reactive chemicals known as oxygen-free radicals or ROS, as well as RNS. The production of free radicals is associated with damage caused to cell structures and the pathogenesis of central nervous system (CNS) conditions, such as Parkinson's disease, stroke, dementia, and epilepsy [18, 19]. The CNS is highly sensitive to O&NS due to its high oxygen consumption and the low activity of antioxidant defenses [20, 21].

The CNS has an extraordinary metabolic rate consuming approximately 20% of all inhaled oxygen at rest; however, it only accounts for 2% of body weight [22]. This enormous metabolic demand is due to the fact that neurons are highly differentiated cells and need large amounts of ATP in order to maintain ionic gradients across cell membranes and for neurotransmission. Since most neuronal ATP is generated by oxidative metabolism, neurons depend critically on mitochondrial function and on oxygen supply [23].

The mitochondria have critical functions which influence neuronal excitability, including the production of adenosine triphosphate (ATP), fatty acid oxidation, excitotoxicity, apoptosis and necrosis control, amino acid cycle regulation, biosynthesis of neurotransmitters, and regulating the homeostasis of cytosolic calcium. Mitochondria are the main site of ROS production and are therefore extremely vulnerable to oxidative damage [24].

3. Reactive Oxygen Species and Reactive Nitrogen Species

Hydroxyl ($HO^{\bullet}$) is the most damaging free radical to cells. It is unstable, with an average life of milliseconds, and therefore it is rarely captured *in vivo*. These radicals often attack molecules by hydrogen abstraction and addition to unsaturation. Intensive and frequent attacks promoted by this radical cause damage to DNA, RNA, proteins, lipids and cell membranes of the nucleus and mitochondria [25, 26].

Superoxide ($O_2^{-\bullet}$) production occurs mainly inside the mitochondrion during the electron transport chain (ETC) when a small number of electrons escape forming $O_2^{-\bullet}$ anion. Measurements of submitochondrial particles demonstrate that between 1–3% of all ETC electrons escape to generate $O_2^{-\bullet}$ instead of contributing to reduce oxygen to water. ETC complexes I and III are responsible for producing $O_2^{-\bullet}$ [27]. Superoxides are relatively unstable, with a half-life

of only milliseconds. Because they are charged, they do not easily cross cell membranes although it may reduce ionic iron and its protein complexes and cause damage to amino acids or loss of protein function [28]. On the other hand, hydrogen peroxide (H_2O_2) molecules do not contain an unpaired electron and thus they are not a free radicals species. In physiological conditions, the production of H_2O_2 is estimated to account for about ~2% of the total oxygen uptake by the organism [25]. Although H_2O_2 is not a free radical, it is extremely harmful because it works as an intermediate in $HO^{\bullet}$ producing reactions, such as Fenton's reaction [29]. Hydrogen peroxide has a long half-life and is able to cross several lipid layers and react with transition metals and some hemoproteins. It can also induce chromosomal alterations, break the deoxyribonucleic acid (DNA) column and, in the absence of catalysts, oxidize sulfhydryl compounds (–SH) [30].

Nitric oxide is a relatively abundant free radical that operates as an important biological signal in several physiological processes, including neurotransmission, blood pressure regulation, body defense mechanisms, smooth muscle relaxation, and immune regulation [25]. The NO has low reactivity with most biomolecules but reacts easily with other free radicals. Nitric oxide is not sufficiently reactive to attack DNA directly, but it may react with $O_2^{-\bullet}$ produced by phagocytes generating peroxynitrite.

Peroxynitrite, on the other hand, is the product of the diffusion-controlled reaction of NO with $O_2^{-\bullet}$ radical. Peroxynitrite is a short-lived oxidant species that is a potent inducer of cell death [31]. As for NO, it may undergo secondary reactions forming agents that may nitrate aromatic amino acids, for instance, tyrosine generating nitrotyrosine and DNA bases, especially guanine [32].

The harmful effects of free radicals to the organism induce several defense mechanisms against O&NS. Such mechanisms include removal of free radicals by catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and nonenzymatic antioxidants [33]. Under normal conditions there is a balance between O&NS and antioxidant action, both with respect to action at the intracellular level. This is essential for organism survival and health [27, 34].

4. Enzymatic Antioxidants

The role of SOD is to protect aerobic cells against $O_2^{-\bullet}$ action. It catalyzes $O_2^{-\bullet}$ dismutation reaction into H_2O_2 and $O_2^{-\bullet}$. There are three known types of SOD: copper-zinc SOD (CuZnSOD), manganese SOD (MnSOD), and extracellular SOD (ECSOD) [33].

Copper-zinc SOD is present mainly in cytoplasm and in some organelles called peroxisomes. This enzyme specifically catalyzes the dismutation of $O_2^{-\bullet}$ anion into H_2O_2 and $O_2^{-\bullet}$ in a pH-independent medium (5–9.5) [35]. Manganese SOD is the mitochondrial form of this dismutase. Its active site contains manganese and reduces the $O_2^{-\bullet}$ generated during the ETC. The amount of MnSOD inside the cell varies according to the number of mitochondria found in each cell type. This enzyme has antitumor activity [25, 33]. Extracellular SOD also contains copper and zinc in its structure and is the main extracellular SOD. It is synthesized inside the cells and secreted into the extracellular matrix [36].

Catalase is an enzyme that reacts very effectively with H_2O_2 to form water and molecular oxygen and with H donors (methanol, ethanol, formic acid, or phenols) with peroxidase activity. Catalase protects cells against H_2O_2 generated inside them. Although CAT is not essential to some cell types under normal conditions, it has an important role in the acquisition of tolerance to O&NS in cellular adaptive response [36, 37].

Glutathione peroxidase is an enzyme that contains a single selenocysteine (Sec) residue in each of four identical subunits, which are essential to the enzyme's activity. Humans have four different GPX types: (1) a classic cytosolic form; (2) a membrane-associated GPx phospholipid H_2O_2; (3) another cytoplasmic enzyme, gastrointestinal GPx; and (4) an extracellular type. All GPx enzymes are known to add two electrons to reduce peroxides by selenols forming (Se-OH) [28]. GPX antioxidant properties allow them to eliminate peroxides as potential substrates for Fenton's reaction. Glutathione peroxidase works together with glutathione tripeptide (GSH), which is present in cells in high (micromolar) concentrations. The substrate for the GPx catalytic reaction is H_2O_2 or organic peroxide ROOH. Glutathione peroxidase catalyzes hydroperoxide reduction using GSH, thus protecting mammalian cells against oxidative damage. Glutathione metabolism is one of the most important antioxidant defense mechanisms [25, 34, 36]. Together with classic H_2O_2-removing enzymes (CAT and GSH-Px), the enzyme thioredoxin reductase (TrxR) is a selenoflavoprotein which forms the thioredoxin system together with the protein thioredoxin (Trx) and NADPH. This is an effective system to reduce proteins in disulfide form and it also participates actively in the removal of H_2O_2 and other peroxides [38]. Thioredoxin reductase catalyzes the reduction of Trx especially, but in humans it can also reduce other substrates, such as vitamin C. This reductase also catalyzes the reduction of disulfide proteins and it is involved in countless vital processes, such as DNA synthesis and the regulation of apoptosis [39]. Additionally, this system also donates electrons during DNA synthesis [40], and Bjornstedt et al. have discovered that NADPH and human TrxR by themselves or with Trx are efficient electron donors to this human plasma peroxidase [41], which allows this enzyme to reduce hyperoxides even when there are low levels of GSH available [42].

There are three identified TrxR isozymes: cytosolic (TrxR-1), mitochondrial (TrxR-2), and a third isoenzyme which has been isolated from the mitochondrion of rat testes (TrxR-3) [43]. TrxR-1 has a wide substrate specificity, since it is responsible for reducing not only Trx but also hydroperozides [44], lipoic acid, ubiquinone, and dehydroascorbate [43]. Thus, the Trx system is regarded as having a crucial role maintaining a cell's redox state. It may also have a role in the system which regulates the expression of redox-sensitive genes through the activation of transcription factors [43].

Coenzyme Q10, in turn, is a liposoluble ubiquinone which has a long isoprenoid side-chain. Ubiquinone is an endogenously-synthesized lipid which has a redox function [45]. Although it is unique and specific, coenzyme Q10 is biosynthesized by all cells and is the main component of the internal mitochondrial membrane, Golgi complex membrane and lysosome membrane. However, its concentration in the membrane of low-density lipoprotein (LDL) particles is low [46]. This variation in distribution suggests different functions for different biological membranes. Ubiquinone taken as a food supplement is distributed mainly between the liver and blood plasma; it is not absorbed by membranes which have high concentrations of this compound. Its reduced form ubiquinol-10 (CoQH2) is a hydroquinone which is found predominantly in the heart, kidneys, and liver. Its oxidized form ubiquinone (CoQ10) is abundant in the brain and intestines [47]. Ubiquinone's main function occurs in the internal mitochondrial membrane where it is involved in the electron transport chain and H+ proton translocation in the mitochondrion, together with cytochromes and mitochondrial dehydrogenases. Dehydrogenases oxidize NADH, NADPH, and FADH2 and transfer protons and electrons to ubiquinone, converting it into ubiquinol. The latter then transfers protons to the mitochondrial matrix and electrons to cytochromes. Thus, cytochromes reduce $O_2^{-\bullet}$ to H_2O with electrons and protons from the matrix. This entire process is essential to produce ATP [46].

However, ubiquinone's redox cycle can also transfer unpaired electrons to acceptors that do not take part in the respiratory chain. Ubiquinol's oxidation occurs through the donation of hydrogen to a free radical, thus generating the respective semiquinone. When oxidation continues, it leads to the formation of ubiquinone with final deactivation of two free radicals. Therefore, this compound is high in antioxidant powers through free radical scavenging; it is also efficient interrupting free radical chain reactions. Such activity is limited to the liposoluble medium due to its long side chain [46].

5. Nonenzymatic Antioxidants

Vitamin C is a hydrosoluble antioxidant, which facilitates its diffusion into intra- and extracellular matrices. Its antioxidant potential is related to direct removal of $O_2^{-\bullet}$ and $HO^{\bullet}$. Furthermore, it contributes to regenerating oxidized vitamin E; however, vitamin C also has prooxidant activity. It may be the one compound, in addition to $HO^{\bullet}$, that can convert Fe^{3+} into Fe^{2+}, which then reacts with H_2O_2 to form OH [25, 33].

Vitamin E (α-tocopherol) scavenges the chain-carrying peroxyl radicals rapidly and interrupts the chain propagation [48, 49]. During this reaction, vitamin E becomes a free radical called tocopheryl, which is less reactive than the lipid radical and migrates to the surface of the membrane to be transformed again into tocopherol through the action of ascorbic acid. However, in elevated concentrations the tocopheryl radical may act as prooxidant [25, 33].

On the other hand, β-carotene is a hydrophilic precursor of vitamin A and large concentrations accumulate in the membranes of certain tissues. Its antioxidant activity is related to the removal of $O_2^{-\bullet}$ and free radicals formed during lipid peroxidation [33, 49]. This activity is due to its conjugated double-bonded structure that can dislocate unpaired electrons, which enables β-carotene to physically quench singlet oxygen without degradation [25].

GSH is present in cytosol, in the mitochondrion, as a cofactor in glutathione reduction cycle through hydrogen atom donation during peroxide reduction by GSHPx, transforming into oxidized glutathione (GSSG). GSH in the nucleus maintains the redox status of sulfhydryl proteins which are necessary for DNA expression and repair [50].

Flavonoids have the ideal structure for radical scavenging. They are more efficient antioxidants than vitamins C and E. Flavonoid antioxidant activity depends on its structure and may be determined by five factors: reactivity as a donor agent of H^+ and electrons, stability of formed flavanol radical, reactivity compared with other antioxidants, capacity to chelate transition metals, and solubility and interaction with membranes [48]. Sequestering activity is directly linked to the flavonoid oxidation potential and to the species to be scavenged. The smaller the flavonoid oxidation potential, the greater its activity as a free radical scavenger [48].

6. 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 [51]. The median prevalence of lifetime epilepsy for developed countries is 5.8 per 1,000 and 10.3 per 1,000 for developing countries [52].

6.1. 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 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 [52, 53]. 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

the involvement of neurotransmitters (GABA and glutamate), as well as other alterations in membrane functions, receptors, ionic changes and alteration of neural networks that are involved in epileptogenesis [54].

6.2. Epilepsy and Oxidative and Nitrosative Stress. Production of free radicals has a role in the regulation of biological function, damage to cell structures, as well as in the pathogenesis of central nervous system neurodegenerative diseases, such as Parkinson's disease, stroke, and dementias [18, 19]. Studies suggest that neurodegenerative diseases may develop characteristics of epilepsy with time [55, 56]. Oxidative and nitrosative stress are regarded as possible mechanisms in the pathogenesis of epilepsy [57]. Studies have already verified that status epilepticus changes redox potential and decreases the level of ATP, which can lead to a collapse in brain energy production and supply [58]. Liang and Patel have demonstrated oxidative damage to susceptible targets (protein, lipids, and DNA) caused by persistent seizures (status epilepticus) [59]. Several studies (animal models and genetic studies) have demonstrated an increase in mitochondrial O&NS and subsequent cell damage after persistent seizures [24, 59–64].

Myoclonic epilepsy with ragged red fibers (MERRF) is a rare syndrome characterized by myoclonus, muscle weakness, cerebellar ataxia, heart block, and dementia. MERFF is the first type of epilepsy in which a molecular defect has been identified and linked to the epileptic syndrome [65]. An A to G transition mutation (A8344G mutation) of nucleotide pair 8344 in human mitochondrial DNA (mtDNA) has been identified as the cause of MERRF. This mutation affects the biosynthesis of mitochondrial oxidative phosphorylation proteins [66]. Furthermore, it has been documented that MERRF causes inefficient ATP generation, increased ROS production, and unbalanced genetic expression of antioxidant enzymes [67]. There are data on generalized seizures associated with mitochondrial mutations in several forms of epilepsy including mitochondrial DNA polymerase γ (POLG1) [68] and tRNAPhe (MT-TF) [69]. Several mitochondrial DNA mutations which compromise the mitochondrial respiratory chain or mitochondrial ATP synthesis have been associated with epileptic phenotypes [70].

The use of animal models has made important contributions to our understanding of seizures. For example, the injection of a single dose of the glutamatergic agonist kainic acid (KA) in rats has been shown to provoke status epilepticus (SE). It has been demonstrated that 16 hours after KA injection the enzyme aconitase, which takes part in the Krebs cycle, becomes inactive decreasing the availability of reducing agents, NADH, and FADH2, for the mitochondrial electron transport chain and compromising ATP synthesis [64]. Systemic or intracerebral KA injections may result in consistent epileptic activity. During an experiment in which KA was injected directly into the CA3 area of the hippocampus, an increase in NO synthesis was demonstrated, contributing to cell death by apoptosis in the CA3 area of the hippocampus after the induction of an SE in the experimental temporal lobe [71]. Therefore in the KA induction model there is an increase in ROS production, mitochondrial dysfunction, and apoptosis of neurons in several areas of the brain, especially those in the hippocampus [72]. Another study which used KA in the CA3 region produced seizures and decreased activity of nicotinamide adenine dinucleotide cytochrome c reductase (NCCR), a marker for ETC's complexes I and III. This was observed in the entire hippocampus 180 minutes after induction [73].

Pilocarpine (a muscarininc agonist) is another chemical induction model. Through excitotoxic stimulation it results in excessive ROS production, formation of lipid peroxidation and nitrite in the hippocampus, striatum and frontal cortex. Pilocarpine is regarded as an appropriate model to study temporal lobe epilepsy (ELT). Animals are systematically treated with a dose of pilocarpine which induces an acute crisis of the limbic system. Status epilepticus usually resolves with the administration of diazepam. This acute intoxication is followed by a period of "latency" (i.e., seizure-free), which usually lasts between 1-2 weeks. It is soon followed by a condition of chronic spontaneous seizures, similar to human ELT. From the pathological perspective, animals treated with pilocarpine show alterations that are very similar to hippocampal sclerosis, a condition that is similar to most ELT patients. There is evidence to support an increase in ROS production in SE induced by pilocarpine or KA, producing considerable amounts of $O_2^{-\bullet}$ and overloading endogenous protection mechanisms (GPx, SOD, and CAT). This results in oxidative damage to proteins, phospholipids, and mitochondrial DNA [74]. Furthermore, there are recent data demonstrating the involvement of mitochondrial OS in oxidative damage to DNA, which can occur in different stages of epileptogenesis triggered by pilocarpine or KA [24].

A model with knockout animal shows the connection between OS and epilepsy. It shows the importance of $O_2^{-\bullet}$ endogenous mitochondrial detoxification when an animal (MnSOD-null) has the MnSOD enzyme removed and shows severe pathologies, while animals with MnSOD superexpression (SOD2) have shown better neuronal survival to KA-induced SE [75].

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 [76]. Although mitochondrial production of H_2O_2 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" [24]. 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 lithium-pilocarpine induced SE and to become permanently damaged during epileptogenesis and chronic epilepsy, even when

H_2O_2 production measurements and mtDNA damage return to control levels [73]. This may contribute to significant mitochondrial dysfunction, harming neuronal excitability through ETC dysfunction and decreased ATP production. Damage to mtDNA and abnormal mitochondrial H_2O_2 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 [76]. Such evidence raises an intriguing possibility that mitochondrial dysfunction caused by the production of free radicals may increase susceptibility to seizures [77].

Mitochondrial dysfunction and O&NS mechanisms during epileptogenesis remain obscure. Since mitochondrial oxidative phosphorylation is the main source of ATP for neurons and the mitochondrion has a role in the homeostasis of intracellular calcium, its dysfunction may strongly affect neuronal excitability and synaptic transmission [77]. Thus, decreased intracellular ATP levels and changes to the homeostasis of neuronal calcium may be factors that contribute to increased susceptibility to epileptic seizures associated with mitochondrial dysfunction. Those changes strongly affect neuronal excitability and synaptic transmission, whose purpose is to be highly relevant to the generation of seizures [78]. Walbaum and Patel propose a model linking acute alterations to chronic epilepsy, while Costello and Delanty believe that epilepsy is a dynamic process characterized by a "latency" period of epileptogenesis after brain damage in, for example, a head injury that occurs prior to the first unprovoked seizure. Subsequently, the risk of new seizures is increasingly higher and, therefore, "seizures could generate seizures" [79].

6.3. Antiepileptic Drugs. The use of antiepileptic drugs (AEDs) with possible neuroprotective effects has been investigated in human or animal models of excitotoxic/non-excitotoxic insults [80]. Classically, the primary objective of epilepsy control has focused on suppressing seizure activity after epilepsy has developed, but the challenge remains to control acquired epilepsy by preventing epileptogenesis, the process by which the brain becomes epileptic [81].

In a review article about the effects of antiepileptic drugs in experimental models of epileptogenesis, Augustín Legido used the kindling model, which involves repeated subconvulsive electrical stimulation to the brain, leading to spontaneous seizures. Classic drugs such phenobarbital, diazepam and valproic acid were more effective attenuating epileptogenesis than phenytoin and carbamazepine (which was practically ineffective). Ethosuximide only had a positive effect on a single model (PTZ). The new antiepileptic drugs, vigabatrin, levetiracetam, tiagabine, and zonisamide, attenuate seizures. In corneal kindling of rats, levetiracetam even protects against epileptogenesis. Felbamate has a slight effect; lamotrigine and topiramate are ineffective [82]. Animal studies about the effect of phenytoin on brain lipid peroxidation initiated by a free radical generating mechanism have shown that phenytoin treatment prevents the occurrence of convulsive and EEG seizures; however, lipid peroxidation was unaffected [83].

Temkin conducted a meta-analysis on the effects of AEDs on seizure prevention and contrasting their effectiveness on provoked versus unprovoked seizures. Data on seven drug trials or combinations for preventing seizures associated with fever, alcohol, malaria, perinatal asphyxia, contrast media, tumors, craniotomy, and traumatic brain injury were evaluated. In conclusion, AEDs were effective or had promising results predominantly for provoked (acute, symptomatic) seizures. For unprovoked (epileptic) seizures, no drug has been shown to be effective, and some have had a clinically important effect ruled out [84].

On the other hand, Hamed and Abdellah reviewed the relation between essentials elements of brain homeostasis (trace elements, electrolytes, membrane lipid peroxidation and antioxidants), neuronal excitotoxicity, and AEDs. The authors identified different effects among AED treatments in which carbamazepine (CBZ) was found to be a better antiepileptic for the control of free radical-related seizures and the level of trace elements were better regulated with CBZ than with valproate (VPA) and phenytoin (PHT) therapies [85].

In a review article of neuroprotection, antioxidants, free radicals, oxidative stress and AEDs, Azam et al. concluded that the use of free radical scavengers in the treatment of epilepsy has provided important perspectives that will be the driving force for future drug design of novel antiepileptics. Although there have been new drug developments for epilepsy, the failure rate of neuroprotective therapies in clinical trials is high [80].

According to Schmidt and Löscher, there have been a number of clinical trials that have failed to prove any significant antiepileptogenesis effects of a several AEDs in posttraumatic epilepsy. Such results may indicate the need to improve understanding of the basic mechanisms of epilepsy. Mechanisms involved in ictogenesis (i.e., initiation, amplification, and propagation of seizures) differ from those involved in epileptogenesis. As for prevention of epilepsy, it is important to identify diagnostic and surrogate markers that help identify who needs prophylaxis, that is, which patients will develop epilepsy after an insult [86].

In [81] Temkin et al. concluded that until some drugs demonstrate a clear antiepileptogenic effect in clinical trials, the best course to reduce the incidence of epilepsy is primary prevention (wearing helmets, wearing seat belts, or decreasing the risk of stroke by reducing smoking) [81].

6.4. Epilepsy and Antioxidants. Induced seizures may be partially prevented with treatment using antioxidant substances, such as SOD mimetics, melatonin e vitamin C [18]. 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 [18] 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 [18].

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 [87].

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 [88].

Wojtal et al. reviewed the role of NO in the anticonvulsant action of AEDs. The influence of various NO synthase inhibitors (NOSIs) on AED anticonvulsant activity was tested in experimental animal epilepsy models. The results showed that some NOSIs were able to modify (through potentiation, inhibition or lack of effect) the anticonvulsive properties of AEDs, but the effects of NOSI were not reversed by L-arginine, an NO precursor [89].

6.5. Oxidative and Nitrosative Stress Pathways, Inflammation, and Neurogenesis in Epilepsy and Ageing. As reported in the introduction section O&NS pathways are induced by inflammatory responses, and subsequent mitochondrial metabolic processes generate highly reactive free radical molecules.

Inflammation, in turn, appears to play a central role among the various processes that have been connected to brain aging. Age-related increases in the activation of glial cells [90–92] as well as age-related increase in cytokines and their receptors [93] documented by histology and gene expression analysis [94–96] indicate widespread inflammatory responses in the aged brain. The increase in inflammatory response observed in the aged brain is associated to structural changes (reduction in neuronal size and a loss of white matter) and impaired functions in areas such as the prefrontal cortex [97] and temporal lobe [98], which is related to a progressive decline of the cognitive and memory functions as well as epilepsy [98].

Prospective studies suggest that inflammatory markers (e.g., high-sensitivity C-reactive protein, interleukin-6, fibrinogen) are important predictors of adverse cognitive outcomes and recent reports link inflammatory biomarkers to age-accelerated cerebral atrophy as well [99]. Indeed, chronic epilepsy appears to be associated with an increased risk of exposure to inflammatory risk factors linked with abnormal cognitive aging and dementia. Evidence that persons with epilepsy may be particularly vulnerable to inflammation comes from both human and animal studies. For example, experimentally-induced seizures trigger a prominent inflammatory response in neural areas involved in the onset and propagation of seizures [100, 101]. Increased inflammatory markers have been detected in serum, CSF, and brain of people with epilepsy. There are relevant findings of increased IL-6 following recent tonic-clonic seizures [102, 103]. This cytokine has also been reported to be elevated secondary to carbamazepine but not valproic acid treatment [104] and elevated levels of fibrinogen have been reported in chronic epilepsy [105].

According to Ekdahl et al., 2003, the suppression of hippocampal neurogenesis by microglia activation contributes to cognitive dysfunction in aging, dementia, epilepsy, and other conditions leading to brain inflammation. These authors' report suggests anti-inflammatory treatment as a possible novel strategy to improve the efficacy of neuronal replacement from endogenous precursors in stroke and other neurodegenerative disorders [106].

Overall, there is an intrinsic relationship between oxidative stress and inflammation in aged people, as a source of hippocampal neurogenesis decline, leading to neurodegenerative diseases, such as epilepsy. Thus, these mechanisms must be further explored in the clinical management of these conditions.

6.6. Epilepsy and the Elderly. Several studies have demonstrated increased incidence and prevalence of epilepsy in older age groups [107–109]. Epilepsy is the third most common type of brain disease in old age, after stroke and dementias [110, 111].

Epilepsy in the elderly is usually the expression of an underlying brain condition. Symptomatic epilepsy in young adults is usually the result of trauma during birth, congenital malformations or brain development anomalies, encephalitis, head trauma or a brain tumor. In elderly individuals epilepsy is caused by stroke or a neurodegenerative disease. However, etiology remains unclear in at least a third of all elderly cases. Elderly individuals (60 or older) who have no other risk factor (prior stroke, trauma, or dementia) have a risk of 1.1%. This might seem small, but it is double the risk of corresponding young adults. Stroke is the main etiology of epilepsy in elderly individuals. Epidemiological studies have demonstrated that a stroke increases the likelihood of a seizure by 23 times and the risk of epilepsy in the first year after stroke increases by 17 times when compared with the risk in the comparable average population [112]. When the

seizure occurs within the first hours to two weeks after the stroke, this is due to acute biochemical abnormalities, for instance, the action of excitatory neurotransmitter glutamate [113]. Late seizures are usually due to chronic processes, such as the removal of inhibitory influences, scars and the formation of new synaptic connections [112].

Stroke and other vascular disasters are the most common risk factors for epilepsy in the elderly [114]. Epidemiological studies show that incidence of neurodegenerative diseases (e.g., Alzheimer's dementia) is increasing. In Europe, the prevalence of dementia is estimated to be approximately 6–8% after 65 years of age and may rise to 20–30% in subjects older than 85 years. [115–117]. A diagnosis of Alzheimer's dementia or other dementia types was associated with at least a six-fold increased risk of unprovoked seizure [118].

Investigating the links between stroke, epilepsy, and dementia, Cordonnier et al. confirmed the hypothesis that patients with stroke who have epileptic seizures without dementia have an increased risk of new-onset dementia [119]. In another study they showed that stroke patients with preexisting dementia have an increased risk of late seizures [120].

A stroke can be caused by rupture of atherosclerotic plaques in the arterial wall. The development of atherosclerotic lesions is the result of a cascade of cellular and molecular events that can be well characterized as a chronic immune-mediated inflammation [121].

Lipid metabolism is of particular interest due to its high concentration in the CNS. In a review article about the effects of altered lipid metabolism on the mechanism of brain injury and disorders, Adibhatla and Hatcher describe the importance of atherosclerosis that results from accumulation of LDL-derived lipids in the arterial wall. Lipids have been associated with the physiopathology of many neurological disorders and neurodegenerative diseases [122].

The sequence of events of cerebral ischemia start with loss of energy, which results in excessive release of neurotransmitters; elevated stimulation of glutamate receptors results in elevated intracellular Ca++ and activation of phospholipase A2 (PLA2) [123]. The activation of PLA2 results in hydrolysis of membrane phospholipids and release of free fatty acids including arachidonic acid, a precursor of important cell-signaling eicosanoids [124]. ROS is produced by the metabolism of arachidonic acid reacting with cellular lipids to generate lipid peroxides. ROS can also be formed nonenzymatically (autoxidation of catecholamines) [122]. ROS produces oxidization of the polyunsaturated fatty acids, resulting in the production of conjugated aldehydes. The most studied aldehyde is 4-hydroxy-2-nonenal (HNE). [125]. HNE is considered a potential inducer of apoptotic cell death and induces cellular dysfunction by many mechanisms (extracellular calcium uptake, GSH depletion, alteration of mitochondrial function leading to the release of cytochrome c and subsequent activation of the caspase cascade and loss of proteasome function) [126]. In a study demonstrating that cellular apoptosis may activate an inflammatory response, resulting in more oxidative damage, Rong et al. investigated the effect of a synthetic superoxide dismutase/catalase mimetic (EUK-134) on indices of oxidative stress as well as on pathological manifestations produced by kainic acid-induced seizure (KA). EUK-134 prevented oxidative stress and attenuated rat brain damage induced by KA and showed that kainate-induced excitotoxicity is caused, at least in part, by the action of reactive oxygen species. Also, oxidative stress occurs before significant neuronal death in the hippocampus [87]. In summary, increased ROS production started a pathological cycle with loss of antioxidant defenses leading to progressive cell damage, which further increase the production of free radicals provoking damage to all components of the cell (proteins, carbohydrates, nucleic acids, and lipids). This leads to cellular death, producing an increase in oxidative stress. This cycle can lead to progressive decline in physiological function and ultimately cell death [122].

Epidemiological studies showed that increased circulating levels of lipoprotein-associated phospholipase A2 predict an increased risk of stroke [127]. 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 [128].

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 [108, 109]. This may be due to an increased excitability of primary hippocampal neurons seen with age [129, 130]. 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.

7. Conclusions and Future Directions

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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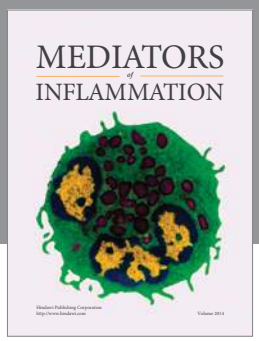

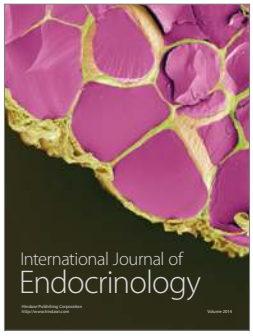

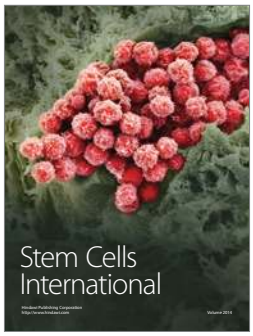

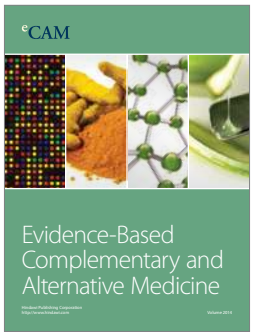

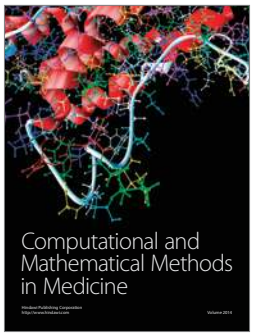

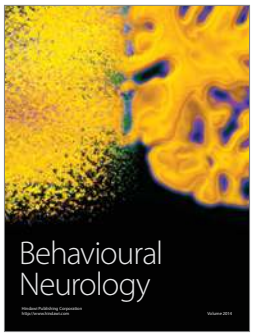

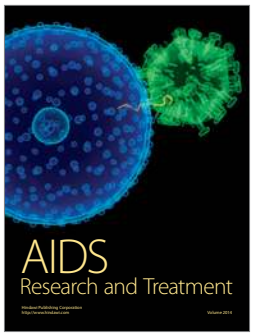

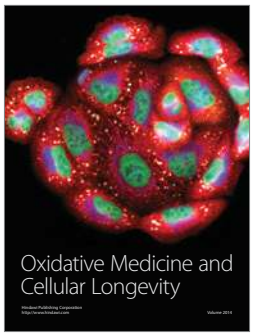

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