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OXIDATIVE STRESS IN ADULT NEUROGENESIS AND IN THE PATHOGENESIS OF ALZHEIMER DISEASE

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9.1 INTRODUCTION

Alzheimer disease (AD) is the most common form of dementia among the elderly. It is a neurodegenerative disease that affects more than 26 million patients worldwide and for which there is still no cure [1, 2]. AD is characterized by memory and cognitive deficits, amyloid deposits, neurofibrillary tangles, neurodegeneration, aneuploidy, and genome damage [3]. Genetic mutations and genetic, acquired, and environmental risk factors, particularly neuroinflammation and oxidative stress, are the main causes of AD [4]. New research in adult neurogenesis and neural stem cells (NSCs) suggests that newly generated neuronal cells of the adult brain, particularly of the hippocampus, may be involved in AD and may be affected by reactive oxygen species (ROS) and oxidative stress [5, 6].

ROS are free radical reactive substances formed by the incomplete reduction of oxygen. They include superperoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\bullet}$) and peroxynitrite anions ($ONOO^-$). Free radicals, such as ROS, are produced physiologically by cells and are involved in cell signaling and metabolism [7]. They are also damaging and toxic to the cells. They oxidize cytoplasmic and membrane proteins, lipids, and nucleic acids. Oxidation of proteins and nucleic acids and peroxidation of lipids compromise cellular functions. Cells are protected against the toxicity of ROS by enzymes, such as superoxide dismutase, catalase, and glutathione. These enzymes act as natural antioxidants. Under physiological conditions, the balance between the generation and degradation of ROS by cells and organisms is highly regulated. Oxidative stress occurs when the level of free radicals exceeds the antioxidant capacity of the cells [8]. It results from an elevation of production of free radicals, from a decrease in the scavenging of free radicals, or from a decrease in the mechanisms used to repair oxidized macromolecules. Oxidative stress and the excessive production of ROS are deleterious conditions leading to cellular dysfunction and cell death, via apoptosis or necrosis [9]. Oxidative stress plays a key role in the development of numerous pathologies, particularly neurodegenerative diseases such as AD [9]. In this chapter we review and discuss the involvement and contribution of oxidative stress and ROS to adult neurogenesis and to the pathogenesis of AD.

9.2 ALZHEIMER DISEASE

AD is a neurodegenerative disease characterized by memory and cognitive deficits and anosmia [10–12]. The disease is initially associated with the loss of nerve cells in areas of the brain that are vital to memory and cognition, such as the entorhinal cortex, hippocampus, and neocortex. As the disease progresses, other regions of the brain are affected, leading to severe incapacity and death, [12]. AD is characterized in the brain by the presence of amyloid plaques and neurofibrillary tangles, the histopathological hallmarks of the disease, and

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aneuploidy [13]. AD is the most common form of dementia among the elderly. The disease affects 30% of individuals over the age of 80 [14]. Age is the principal risk factor for AD. The incidence of the disease doubles every 5 years after age 65 [14]. AD affects more than 35 million patients worldwide, a number expected to quadruple by 2050 as the population ages [15]. Late-onset AD (LOAD) refers to cases of AD diagnosed after the age of 65. Early-onset AD (EOAD) refers to cases of AD diagnosed before age 65. LOAD accounts for the vast majority, over 93%, of all cases of AD.

9.2.1 Inherited and Sporadic Forms of Alzheimer Disease

The inherited form of AD, also known as familial Alzheimer disease (FAD), is caused by mutations in so-called familial Alzheimer genes, such as the gene of β-amyloid precursor protein (APP), the presenilin-1 (*PSEN-1*) gene, and the presenilin-2 (*PSEN-2*) gene [16]. It is a rare form of the disease, affecting about 200 families in the world. The sporadic form of AD is caused by a combination of genetic, acquired, and environmental risk factors [17]. These include the presence of the ApoE varepsilon 4 allele (*ApoE4*), the presence of variants in at least two different clusters of intronic sequences in the neuronal sortilin-related receptor (*SORL1*) gene, hypertension, diabetes, neuroinflammation, and oxidative stress [18–21]. The sporadic form of AD is the most common form of the disease. It accounts for most cases of LOAD, whereas the inherited form of AD accounts for most cases of EOAD.

9.2.2 Amyloid Plaques and Neurofibrillary Tangles

Amyloid plaques and neurofibrillary tangles are deposits of proteins distributed throughout the brain of patients with AD, particularly in the regions of degeneration such as the entorhinal cortex, hippocampus, and temporal, frontal, and inferior parietal lobes [22]. Amyloid plaques are primarily composed of extracellular aggregates of protein β-amyloid or amyloid fibrils and of the serine protease inhibitor α1-antichymotrypsin [22]. Protein β-amyloid is a 42-amino acid peptide that is derived from the posttranscriptional maturation of APP [23]. The abnormal processing of APP results in the aggregation of protein amyloid and the formation of amyloid plaques. Neurofibrillary tangles are intracellular aggregates of hyperphosphorylated Tau protein. Tau protein is a microtubule-associated phosphoprotein [24]. The hyperphosphorylation of Tau protein by kinases results in the aggregation of Tau protein and the breakdown of microtubules that are involved in cell structure, intracellular transport, and cell division [25]. Amyloid plaques and neurofibrillary tangles are two of the probable causes of the pathogenesis of AD; amyloid plaques and neurofibrillary tangles that would cause cell death in the brain [26]. In support of this contention, rat embryonic cortical neurons cultured with toxic concentrations of protein β-amyloid reenter the cell cycle and die by apoptosis in vitro [27].

9.2.3 Aneuploidy and Expression of Proteins of the Cell Cycle

Aneuploidy is a landmark of AD pathology. Preparations of lymphocytes from patients with AD, EOAD and LOAD, reveal an increase of aneuploidy in cells, particularly for chromosomes 13, 18, and 21 [28, 29]. Since the cells that are the most likely to develop aneuploidy are dividing cells, the nondisjunction of chromosomes during cell division in stem cells or somatic cells that retain their ability to divide is at the origin of aneuploidy in lymphocytes of patients with AD [30]. A substantial number of neurons, 4% to 10%, in regions of degeneration, such as the hippocampus, of the brain of AD patients express proteins of the cell cycle and are aneuploid. Among the proteins of the cell cycle expressed by nerve cells in regions of degeneration are the proliferating nuclear antigen, Ki-67, cyclin D, cyclin-dependent kinase 4, and cyclin B1 [31, 32]. Nerve cells are postmitotic. The forced expression of oncogenes in postmitotic nerve cells causes cell death rather than cell proliferation. Hence, nerve cells in regions of degeneration that express proteins of the cell cycle or are aneuploid would originate from abortive cell cycle reentry, leading to apoptosis, or cycle reentry and gene duplication, without cell division, leading to aneuploidy [33, 34].

The deregulation and/or reexpression of proteins controlling the cell cycle and aneuploidy in nerve cells would underlie the neurodegenerative process and pathogenesis of AD. In aneuploid cells, the genetic imbalance results in the overexpression of genes by the cells. This has tremendous consequences for the development of AD, as genes involved in the pathology of AD would further contribute to the pathogenesis of the disease, as a result of their overexpression. The genes of ApoE, APP, PSEN-1, PSEN-2 and TAU are located on chromosomes 19, 21, 1, 14, and 17, respectively [35–38]. Aneuploidy for chromosomes 19, 21, 1, 14, and/or 17 would result in the overexpression of ApoE and in an increased risk for individuals who have *ApoE4* in their genetic make-up of developing the sporadic form of AD, would result in the overexpression of APP and promote the formation of amyloid plaques, would promote the formation of amyloid plaques in patients carrying FAD mutations on PSEN genes and contribute to the pathogenesis of EOAD, and/or would result in the overexpression of Tau

TABLE 9.1 Processes Associated with Neurogenesis and Oxidative Stress in Alzheimer Disease

DNA damage	Mutational events, modified base 8-hydroxydeoxyguanosine, strand breaks, and large deletions
Cell cycle	Activity in controlling the cell cycle, cell cycle reentry of nerve cells, aneuploidy, particularly for chromosome 17 carrying the *TAU* gene
Protein oxidation	Enzymatic and mitogenic pathways, such as EGF and VEGF pathways, the stress-activated protein kinases JNK and p38, JAK/STAT, protein kinase C pathways, and histone deacetylase

Oxidative stress is a risk factor for developing Alzheimer disease (AD). Proteins, lipids, and nucleic acids elicit high rate of oxidation in patients with AD. The nuclear and mitochondrial DNA in degenerated regions of the brain of patients with AD elicit lesions. Reactive oxygen species (ROS) and oxidative stress promote cell cycle reentry of nerve cells and aneuploidy, particularly for chromosome 17 carrying the *TAU* gene. Aneuploidy for chromosome 17 in newly generated cells of the adult brain would promote the expression of Tau proteins in the hippocampus and neurodegeneration. ROS and oxidative stress contribute to the pathogenesis of AD by promoting cell death and neurodegeneration.

protein and promote the formation of neurofibrillary tangles. Cells of AD patients elicit an elevation of aneuploidy, particularly for chromosomes 13, 18, and 21 [28, 29, 39]. Hence, aneuploid cells in AD patients are likely to contribute to the pathogenesis of the disease with high probability as a result of the overexpression of genes involved in AD. It is proposed that the genetic imbalance in aneuploid nerve cells signifies that they are fated to die [33]. Their relatively high percentage at any one time in regions of degeneration in AD brains suggests that they will undergo a slow death process, unlike apoptosis. These cells may live in this state for months, possibly up to 1 year [33]. Hence, the deregulation and/or reexpression of proteins controlling the cell cycle in nerve cells would underlie the neurodegenerative process in AD.

9.2.4 DNA Damage

The nuclear and mitochondrial DNA in degenerated regions of the brain of patients with AD elicit lesions and mutational events, such as DNA oxidation, as evidenced by the presence of the modified base 8-hydroxydeoxyguanosine, strand breaks, and large deletions (Table 9.1) [40]. Proteins, lipids, and nucleic acids elicit a high rate of oxidation in patients with AD, particularly in regions containing amyloid plaques and neurofibrillary tangles in the brain [41]. AD is a neurodegenerative disease caused by an excessive rate of damage in the genome [42].

9.3 ADULT NEUROGENESIS AND ENHANCED NEUROGENESIS IN ALZHEIMER DISEASE

9.3.1 Adult Neurogenesis and Neural Stem Cells in Mammals

Neurogenesis occurs primarily in two regions of the adult mammalian brain, the dentate gyrus (DG) of the hippocampus and the anterior region of the subventricular zone (SVZ), in various species including in humans [43–46]. Newly generated neuronal cells in the subgranular zone of the DG migrate to the granule cell layer, where they differentiate into granulelike cells and extend axonal projections to the CA3 region of the Ammon's horn [47, 48]. Newly generated neuronal cells in the SVZ migrate through the rostro-migratory stream to the olfactory bulb, where they differentiate into granule and periglomerular interneurons [49, 50]. Newly generated neuronal cells in the DG establish synaptic contacts and functional connections with neighboring and target cells [48, 51–53]. They establish mossy fiber-like synapses with target cells of the CA3 region of the Ammon's horn [53]. The number of neuronal cells generated in the adult mammalian brain is relatively low. In the DG, it is estimated that 9000 neuronal cells, corresponding to about 0.1% of the granule cell population, are generated per day in young adult mice [54]. In higher primates, such as humans and monkeys, the number of neuronal cells generated per day is lower than in rodents. In adult macaque monkey, an estimated 0.004% of the granule cell population is generated per day in the hippocampus [55]. Newly generated neuronal cells in the adult brain survive for an extended period of time, at least 2 years in the human hippocampus [43]. Newly generated neuronal cells of the adult brain may replace nerve cells born during development. They may be involved in the physiology, pathology, and plasticity of the nervous system, particularly of the hippocampus and olfactory bulb.

Newly generated neuronal cells in the adult brain would originate from a pool of residual NSCs; the self-renewing multipotent cells that generate, through a transient amplifying population of cells, the main cell types of the nervous system, nerve cells, astrocytes, and oligodendrocytes [56, 57]. In support of this contention, self-renewing multipotent NSCs have been isolated and characterized in vitro from various regions of the adult brain of mammals, including from the hippocampus and SVZ [58–60]. Neural progenitor and stem cells express molecular markers, such as the intermediate filament nestin, the transcription factors sox-2, oct-3/4, and the RNA binding protein Musashi 1 [61–64]. Hence,

neurogenesis occurs in the adult brain and NSCs reside in the adult central nervous system. This reveals that the adult brain has the potential for self-repair and may be amenable to repair. The stimulation of endogenous neural progenitor or stem cells of the adult brain and the transplantation of adult-derived neural progenitor and stem cells are proposed to repair and restore the degenerated or injured nerve pathways. To this end, the isolation and characterization of population of neural progenitor and stem cells from human biopsies and postmortem tissues provide a source of tissue for cellular therapy for the treatment of a broad range of neurological diseases and injuries, including neurodegenerative diseases such as AD and Parkinson disease, cerebral strokes, and traumatic and spinal cord injuries [65, 66].

Neurogenesis occurs constitutively in the adult brain and is modulated by a broad range of environmental stimuli, physiological and pathological conditions and processes, trophic factors/cytokines, neurotransmitters, and drugs. This includes environmental enrichment, learning and memory tasks, physical activity, AD, and epilepsy [67, 68]. The contribution of adult neurogenesis and its modulation to the physiology and pathology of the nervous system remains to be determined.

9.3.2 Neurogenesis in Patients with Alzheimer Disease and in Animal Models of Alzheimer Disease

The expression of markers of immature neuronal cells, such as doublecortin and polysialylated nerve cell adhesion molecule, is increased in hippocampal regions, particularly the DG, of the brain of patients with clinical diagnosis of AD [69]. Neurogenesis is enhanced in the DG of adult transgenic mice that express the Swedish and Indiana APP mutations, a mutant form of human APP [70]. It is reduced in the DG of PDAPP adult transgenic mice, a model of AD with age-dependent accumulation of protein β-amyloid, in the DG and SVZ of adult transgenic mice deficient for PSEN-1 and/or APP and in the DG of adult transgenic mice overexpressing variants of APP or PSEN-1 [71–75]. These results show that neurogenesis is enhanced in the hippocampus of the brain of patients with AD, but they report conflicting data and discrepancies in animal models of AD.

The apparent discrepancies in the modulation of adult neurogenesis in humans and in animal models of AD may originate from the validity of animal models as representative of AD and from limitations and pitfalls in the conducted studies. AD is a neurodegenerative disease characterized by widespread neurodegeneration and multiple and complex processes, including the deposit of amyloid, the formation of neurofibrillary tangles, and aneuploidy. Hence, transgenic mice models of AD represent models to study the genes involved in the disease rather than the disease itself. Transgenic mice may be limited in their validity to study adult phenotype, and particularly adult neurogenesis, as the mutated genes may alter the animal's development and this may affect the adult phenotype. Aggregation of protein β-amyloid during development in APP transgenic mice may alter the development of the nervous system and therefore may have adverse consequences on adult neurogenesis [76]. The apparent discrepancies in the modulation of adult neurogenesis in human and animal models of AD as well as discrepancies in studying adult neurogenesis in human and animal models in general, may originate from the methods used for studying and quantifying cell proliferation and neurogenesis. Bromodeoxyuridine (BrdU) labeling has been the most used method to study adult neurogenesis in vivo. BrdU is a thymidine analog used for birthdating and monitoring cell proliferation, as BrdU integrates into the DNA of dividing cells [77]. In this paradigm, BrdU is generally administered peripherally, intraperitoneally in rodents, and the fate of the BrdU-labeled cells is followed by immunohistochemistry [78]. Multiple immunohistochemistry staining with markers of neuronal lineages combined with confocal microscopy and stereology allows qualitative and quantitative study of adult neurogenesis [79–81]. BrdU labeling as a method for studying adult neurogenesis, is not without limitations and pitfalls, particularly for the study of adult neurogenesis in AD. BrdU is not a marker for cell proliferation and neurogenesis, but a marker of DNA synthesis. As a thymidine analog, BrdU integrates into DNA of dividing cells during the S-phase of the cell cycle. Hence, studying cell proliferation and neurogenesis with the BrdU-labeling paradigm requires discriminating cell proliferation and neurogenesis of other events involving DNA synthesis, particularly abortive cell cycle reentry leading to apoptosis and cell cycle reentry and gene duplication without cell division, leading to aneuploidy [82, 83]. Since aneuploidy in the region of neurodegeneration is a landmark of AD pathology, careful analysis must be carried out when studying adult neurogenesis in animal models of AD with the BrdU-labeling paradigm. In addition, the permeability of the blood-brain barrier is affected in AD [84]. As consequence, an increase in BrdU labeling in the brain could originate from an increase in BrdU uptake rather than an increase in cell proliferation and neurogenesis. There are other considerations that may affect the analysis of BrdU-labeling studies. Among these considerations, there is no consensus on the term "neurogenesis." Some studies only present proliferation data, whereas others present only neuronal differentiation or survival data, and in most studies, and in particular in human postmortem studies, only one time point along the pathology is analyzed. Therefore, careful

analysis and discussion of the studies must be carried out when using BrdU labeling to study adult neurogenesis, particularly in AD. Some of these limitations also apply when studying adult neurogenesis by immunohistology against markers of the cell cycle. In particular, immunohistochemistry for proteins of the cell cycle does not allow discrimination among cells reentering the cell cycle as a prelude to apoptosis, cells undergoing DNA duplication without cell division, as part of their pathological fate, and the genesis of neuronal cells [85].

Hence, these studies of adult neurogenesis in the hippocampus of the brain of patients with AD and in animal models of AD remain to be confirmed and validated. Indeed, neurogenesis might be differentially regulated along the pathogenesis. Enhanced neurogenesis in the DG of AD brain would contribute to a regenerative attempt, to compensate for the neuronal loss. It would result from damage or stimulation induction of neurogenesis and may be a consequence, rather than a cause, of the disease [86]. In the SVZ, studies show a reduction in the number of neural progenitor cells in patients with AD, as revealed by immunohistology for the markers of neural progenitor and stem cells, nestin and Musashi1 [87]. The reduction in the number of neural progenitor cells in the SVZ of AD brain may underlie the compromised olfaction associated with the disease.

9.4 OXIDATIVE STRESS: A RISK FACTOR FOR DEVELOPING ALZHEIMER DISEASE

Lipids, proteins, and nucleic acids elicit high rates of oxidation, particularly in regions of degeneration in the AD brain [41]. Oxidative stress is a risk factor for developing AD [9].

9.4.1 ROS and Oxidative Stress Promote Cell Death and Neurodegeneration

Protein β-amyloid promotes the generation of ROS in the brain of AD patients [88]. ROS, particularly generated by protein β-amyloid, and oxidative stress in the brain of patients with AD would contribute to the pathogenesis of the disease by promoting cell death and neurodegeneration. Abnormal mitotic signaling, such as abortive cell cycle reentry leading to apoptosis and cycle reentry and gene duplication, without cell division, leading to aneuploidy, underlies the process of neurodegeneration and contributes to the pathogenesis of AD [33, 34]. It is proposed that oxidative stress and abnormal mitotic signaling would both be necessary to propagate the disease. A "two-hit hypothesis" has been proposed to conciliate the activity of oxidative stress and abnormal mitotic signaling, such as abortive cell cycle reentry and gene duplication without cell division, as causative factors of AD: Oxidative stress and abnormal mitotic signaling can act independently as initiators; however, both processes are necessary to propagate the pathogenesis of AD [89].

Abortive cell cycle reentry, cell cycle reentry and gene duplication without cell division, and DNA damage are underlying processes in the development of AD. ROS and oxidative stress promote cell cycle reentry of nerve cells and DNA damage [90]. The contribution of ROS and oxidative stress to the process of cell cycle reentry of nerve cells would support the "two-hit hypothesis" conciliating the activity of oxidative stress and abnormal mitotic signaling in the brain of AD patients. The mechanism by which ROS and oxidative stress increase the risk of developing AD, particularly through its activity on abnormal mitotic signaling, remains mostly unknown. ROS and oxidative stress would contribute to the pathogenesis of AD through their activity in controlling the cell cycle (Table 9.1). It would increase the risk of developing AD, directly or indirectly, through their oxidative activity on DNA and on various enzymatic and mitogenic pathways, such as the EGF and VEGF pathways, the stress-activated protein kinases JNK and p38, JAK/STAT, protein kinase C pathways, and histone deacetylase and through mutational events including strand breaks and large deletions (Table 9.1) [91]. Studies show that whether ROS-exposed cells undergo proliferation, growth arrest, or apoptosis depends in part on where the cell resides in the cell cycle when insulted [92]. This has implications for the mechanisms by which oxidative stress may affect neuronal cells in the adult brain, whether and how it affects mature neurons or newly generated neuronal cells in regions of neurodegeneration, such as the hippocampus. ROS and oxidative stress would also contribute to DNA damage, if the oxidation of DNA surpasses the DNA repair capacity of the cell, leading to the accumulation of mutations and the loss of genome stability, a landmark of AD pathology.

9.4.2 Oxidative Stress Promotes the Generation of Aneuploid Newly Generated Neuronal Cells in the Adult Brain

Stem cells and somatic cells that retain the ability to divide are the most likely to develop aneuploidy. Since newly generated neuronal cells of the adult brain originate from stem cells, they are most likely to develop aneuploidy. The nondisjunction of chromosomes in the process of cell division of adult neurogenesis would lead to newly generated neuronal cells that are aneuploids or to a population of aneuploid neural progenitor cells that would not proceed with their developmental program in the neurogenic regions, primarily the DG of the

hippocampus and SVZ [93]. The fate of these aneuploid newly generated neuronal cells in the adult brain remains to be elucidated. They may survive for an extended period of time or have their life span shortened, further contributing to the degenerative process in AD.

Aneuploid newly generated neuronal cells that would be aneuploid for chromosomes carrying genes involved in the pathogenesis of AD, such as the *APP*, *PSEN1* and *TAU* genes located on chromosomes 21, 14, and 17, respectively [35–38], would also further promote the development of AD, by promoting the aggregation of protein β-amyloid and Tau protein and neurodegeneration [93]. Oxidative stress promotes aneuploidy, particularly for chromosome 17 carrying the *TAU* gene (Table 9.1) [94]. Hence, ROS and oxidative stress would increase the risk of the generation of newly generated neuronal cells that are aneuploid for chromosome 17, or of a population of neural progenitor cells that are aneuploids for chromosome 17 and would not proceed with their developmental program. Aneuploidy for chromosome 17 in newly generated cells of the adult brain would promote the expression of Tau proteins in the hippocampus, and neurodegeneration. The hyperphosphorylation of Tau proteins would further promote the breakdown of microtubles and the generation of aneuploid newly generated neuronal cells [90]. Hence, oxidative stress would promote aneuploidy and the formation of neurofibrillary tangles in the neurogenic regions of the adult brain, contributing to neurodegeneration and to the pathogenesis of AD [95].

9.4.3 Antioxidants Increase Neurogenesis in the Adult Hippocampus

BrdU labeling studies show that antioxidants, such as curcumin, increase neurogenesis in the hippocampus of adult rodents [96]. This suggests that ROS and oxidative stress may decrease neurogenesis in the adult brain. On one hand, such a decrease would reduce the deleterious activity of ROS and oxidative stress in promoting the generation of aneuploid newly generated adult neuronal cells in the adult brain. On the other hand, it would limit the regenerative potential of adult neurogenesis, particularly in the hippocampus of the brain of AD patients. ROS and oxidative stress would elicit a dual activity on newly generated neuronal cells of the adult brain and on the pathogenesis of AD, promoting aneuploidy and decreasing neurogenesis [95].

9.4.4 Oxidative Stress in Patients with Mild Cognitive Impairment

The level of DNA damage and oxidized DNA bases (pyrimidines and purines) is increased by twofold in leukocytes of patients with mild cognitive impairment and AD, compared to individuals not diagnosed with the diseases [97, 98]. Patients with mild cognitive impairment have a probability to develop AD of 12% per year or 50% within 4 years [99]. Hence, oxidative damage occurs at the early stages of AD, and oxidative stress is a risk factor and contributes to the pathogenesis of the disease [100, 101].

9.5 CONCLUSION

Oxidative stress is an environmental risk factor for developing AD, and oxidative damage occurs at the early stages of AD. Oxidative stress and ROS promote cell death and neurodegeneration and the generation of aneuploid newly generated neuronal cells in the adult brain. Adult neurogenesis is enhanced in the DG of brain of patients with AD, but ROS would reduce neurogenesis in the hippocampus. Reduced neurogenesis by ROS would limit the regenerative capacity of the adult brain and the risk of generating aneuploid newly generated neuronal cells. Further studies are mandated to elucidate the contribution of adult neurogenesis to the pathology and pathogenesis of AD. Further studies are also mandated to confirm and validate the modulation of adult neurogenesis in the brain of patients with AD, and the activity of oxidative stress and ROS on newly generated neuronal cells of the adult brain. Antioxidants have been proposed and considered for the treatment of AD, potentially delaying the development of the disease. These drugs may reduce the deleterious activities of ROS and oxidative stress in the adult brain, and in particular may reduce the generation of aneuploid newly generated neuronal cells. They may also promote the regenerative capacity of the adult brain, particularly in patients with AD.

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