Chapter 6

Oxidative Stress, Inflammation, and Formation of Beta-Amyloid 1-42 in Brain

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Abstract

Alzheimer's disease is characterized by the pathognomonic presence of intracellular neurofibrillary tangles containing hyperphosphorylated tau protein and extracellular senile plaques primarily formed by β-amyloid. Both the neurofibrillary tangles and the plaques formed by β-amyloid 1-42 are the final result of a chain of events that progressed along with the disease for a long time. Oxidative stress plays a fundamental role among those events as proven by the experiments carried out using animal models. This can be demonstrated since there are studies indicating that, although the formation of β-amyloid is inhibited through different mechanisms (using drugs or specific antibodies), cognitive deficit is not prevented. In this chapter, we will focus on reviewing the role the chronic state of oxidative stress plays in the development of Alzheimer's disease and how the loss of redox balance induces a vicious cycle that may change normal signaling. As a consequence, there are alterations in multiple metabolic pathways that end up in the formation of hyperphosphorylated tau and insoluble β-amyloid, leading to the advance of a progressive neurodegeneration process. This is characterized by neuronal dead, astrocytic changes, microglia activation, and the loss of brain repair.

Keywords: oxidative stress, Alzheimer's disease, β-amyloid 1-42, ozone, neurodegeneration

1. Introduction

Despite a great deal of studies and the efforts of researchers in the field, the physiopathology of Alzheimer's disease (AD) is not yet clear. There is neither an accurate early diagnosis nor an effective treatment that allows the patients to have better life expectancies [1]. Perhaps one of the most important problems to solve is understand that when the diagnosis is made, the symptoms and the signs of Alzheimer's disease are the result of a long chain of events that took place during an extended period of time and that such symptoms and signs change with time [2].

One can assume that intracellular signaling and metabolic changes found during the early stages of the disease are not the same as the ones found at more advanced stages. For this reason, recent postmortem studies fail to completely clarify the physiopathology of this disease.

2. Changes at cellular level caused by chronic oxidative stress

Acute oxidative stress is reversible and it is present in a number of physiological and pathological mechanisms that are reversible as well. These mechanisms play a defensive role in the organism during respiratory burst [3]. However, the chronic oxidative stress state is an epiphenomenon that affects the organism and the brain tissue at different levels. It is involved in the maintenance and advance of the chronic degenerative disease that is usually irreversible [4].

2.1. Cell signaling, redox balance, and oxidative stress state

It has been widely demonstrated that in redox balance, the rise in reactive species induces an increase in the production of antioxidant enzymes. In turn, the enzymes rapidly compensate the free radicals, allowing the system to return to redox balance [5]. During this state, free radicals also play a central role signaling the different intracellular cascades related to cell cycle and antioxidant response. The latter is associated to repair mechanisms and cell survival, regulation of inflammatory response, signaling of intracellular metabolic pathways, maintenance of energetic metabolism, and the efficient system of protein degradation by the proteasome [6].

In the brain, insulin signaling over its receptors is crucial to survival maintenance of neural metabolism. Similarly, the correct functioning of phosphorylation and dephosphorylation pathways that takes place during redox balance promotes an efficient functioning of the signaling pathways [7]. We must also include low-density lipoprotein (LDL) receptors, cholesterol, and receptors for advanced glycation end products [8–10].

Nevertheless, the loss of redox balance causes disturbances in the pathways mentioned above changing the signaling and the normal metabolism needed to maintain cell function.

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2.2. Reactive oxygen species and antioxidant defenses

It has been reported that the excess of free radicals formed during normal metabolism is able to produce oxidation in proteins, DNA, and RNA. It also causes lipid peroxidation and sugar modification, thus inducing changes that lead to catastrophic neuronal death in the hippocampus, including neocortex regions [11]. Furthermore, free radicals are chemical species that have one or more unpaired electrons, which can act as acceptors of other electrons belonging to other molecules. As a result, they produce oxidation and cause a chain of molecular damage [12]. Free radicals come from sources that are endogenous (the own metabolism of the cell, mainly carried out during the respiratory chain in the internal membrane of the mitochondria) and exogenous (environmental pollution, tobacco, smoke, drugs, xenobiotics, or radiation) [13]. Despite the deleterious effects of oxidative stress, aerobic organisms have developed a wide variety of mechanisms to maintain genomic stability. These mechanisms include endogenous and exogenous antioxidants that can be divided into enzymatic and nonenzymatic antioxidants [14].

The enzymatic antioxidants are genetically codificated, for example, superoxide dismutase (SOD) cupper/zinc, manganese, glutathion peroxidase, glutathion reductase, and catalase [15]. The nonenzymatic antioxidants such as thioredoxin, vitamin C, vitamin A, and vitamin E have a strong role as scavengers [16].

2.3. Loss of redox balance and oxidative stress state

The free radicals are metabolized in the biological systems leading to the formation of reactive species that, depending on the radical (oxygen, nitrogen, iron, copper, etc.), receive their denomination. For example, the metabolism of the superoxide radical generates the reactive oxygen species (ROS), whereas the metabolism of the nitric oxide radical generates reactive nitrogen species (RNS) [17].

The increase of ROS together with the deficit of antioxidant systems causes a chronic oxidative stress state. It is interesting to point out that an acute increase of the ROS causes a stimulation of the antioxidant systems depending on the antioxidant capability of the organism; this is the basis of ozone therapy [18]. However, the production or the exposure chronic, whether by environmental pollutants or metabolic disorders, to low or moderate ROS concentrations in the organism induces a chronic oxidative stress state. Such state is found in several chronic degenerative diseases among which neurodegenerative diseases as Parkinson's and Alzheimer's are included [19].

The chronic oxidative stress state is an epiphenomenon that affects cell functions at different levels. They go from changes in signaling of the cell cycle [20], response to endogenous antioxidant systems [21], loss of repair and cell function mechanisms [22], and regulation of the dynamic of the cytoskeleton [23]. They also include protein misfolding and oxidation [24], alterations in function and signaling of the endoplasmic reticulum (ER) during protein synthesis and chaperone signaling [25], alteration and loss of cell receptor functionality [26, 27], and mitochondrial damage leading to a deficit of energy [28]. In addition, there is loss of the regulation and selectivity of the cell membrane [29], stimulation of phosphorylation

pathways and inhibition of dephosphorylation pathways, which alter intracellular signaling [30, 31], and finally, the loss of regulation of inflammatory response [32], as is shown in **Figure 1**.

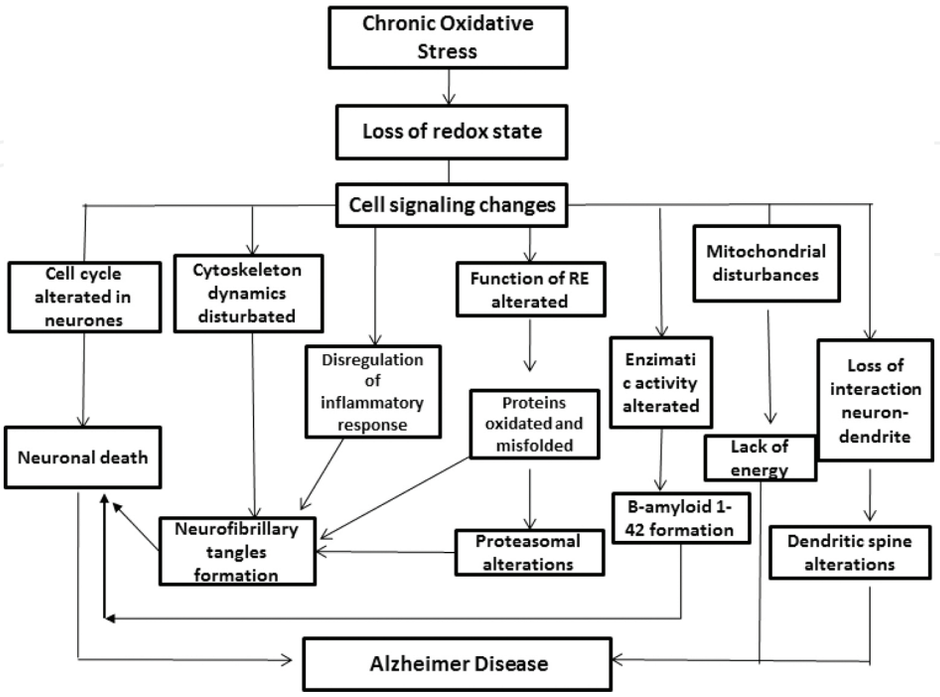

Figure 1. Effect of chronic oxidative stress on intracellular changes present during the development of Alzheimer's disease.

2.4. Cell cycle and oxidative stress

The presence of an oxidative stress state has been associated with an aberrant reentry into the cell cycle, a phenomenon associated with the death of terminally differentiated neurons. This mechanism has been observed in samples from Alzheimer's disease and Down syndrome patients [33, 34]. It has been proven that the increase in the cyclin D2 levels due to the loss of FoxO 1a downregulation on this cyclin may take part of the aberrant reentry into cell cycle. In consequence, the mature neurons do not divide activating cell death mechanisms by apoptosis where caspase-3 might play an important role [35].

2.5. Antioxidant enzyme regulation in an oxidative stress state

The increase of free radicals acts upon a series of pathways that lead to transcription of antioxidant enzymes. Transcription factors within these pathways allow the activation of antioxidant response elements (AREs) in the nucleus [36]. The AREs cause the raise in messenger RNA transcription for the increase in antioxidant enzyme synthesis. For instance, FoxO 3a activation stimulates the signaling pathway for the increase in the synthesis of superoxide dismutase enzymes, particularly the manganese superoxide dismutase, MnSOD [35]. The signaling pathway regulated by the transcription factor Nrf2 is also activated by the presence of ROS. Under oxidative stress conditions, Nrf2 transactivates the synthesis of

hundreds of antioxidant genes such as HMOX-1, NQO-1, GCS, and GSTM1, among others [37]. In humans, the insufficient activation of this transcription factor has been related to chronic diseases as Parkinson's, Alzheimer's, and amyotrophic lateral sclerosis [38]. In brains of Alzheimer's patients, studies have also proven a reduction in the Nrf2 protein levels in hippocampus astrocytes. This is one of the key areas where ROS causes neurodegeneration in this disease [39]. In addition, some target genes of this transcription factor have been found to be reduced in the frontal cortex, as is the case of the protein p62 [40].

2.6. Regulation of the dynamic of the cytoskeleton and the effect of chronic oxidative stress

The neuronal cytoskeleton consists of microtubules, actin filaments, and neurofilaments (intermediate filaments). All these components are regulated through the changes in the levels of expression of the genes that code, posttranslational changes, and the set of proteins with which they interact. Oxidative stress affects the regulation mechanisms of the neuronal cytoskeleton when acting over its components. Because all the components are interconnected and regulate each other, the damage caused by oxidative stress affects the whole cytoskeleton network [41]. The microtubules are particularly susceptible to oxidative stress that causes its depolymerization [42]. Furthermore, oxidative stress affects the tubulin through aberrant posttranslational modifications [43]. For their part, actin filaments are less susceptible to the negative effects of oxidative stress because they use ROS for their reorganization [44]. Finally, neurofilaments are phosphorylated in the presence of reactive species, which causes the formation of protein aggregates as the ones found in neurodegenerative diseases like Alzheimer's [45].

2.7. Misfolding and protein oxidation by chronic oxidative stress

Oxidation can affect protein structure because the endoplasmic reticulum responds to oxidative stress by affecting chaperons and producing protein misfolding altering their spatial structure. This causes negative effects on the functionality of the proteins and makes them susceptible to aggregation, inducing to cell toxicity [46].

The disassembly in the ubiquitin-proteasome proteins is a protection mechanism to avoid the damages caused by oxidative stress [47]. A number of studies have reported that from the 26S proteasome complex, the 20S subunit is more resistant to the damage caused by ROS compared to the 19S subunit. It may bind and degrade misfolded oxidized proteins without the need of ubiquitination and ATP expenditure [48]. However, during a chronic oxidative stress state, proteasomal proteins are also modified by oxidation, thus altering their function and causing intracellular and extracellular protein accumulation [49].

2.8. Alterations in endoplasmic reticulum function and signaling by chronic oxidative stress

The endoplasmic reticulum is the organelle that within their functions include the calcium (Ca^{2+}) storage and protein folding with the participation of different enzymes and chaperones [50]. The redox state inside the ER lumen is highly oxidant and the changes caused by the presence of ROS affect the correct protein folding. It contributes to the breaking of the

disulphide bonds by the binding of reactive species to thiol groups [51]. Misfolded proteins that are formed in the ER cause Ca^{2+} release in the cytoplasmic space. When the mitochondria capture excessive amounts of calcium, it loses the regulation of its membrane, creating a mitochondrial transition pore. This results in ATP deficit and ROS increase which induce, in turn, ER Ca^{2+} release; thus, a vicious cycle in the intracellular regulation of Ca^{2+} levels is created [52]. Studies performed with cerebral samples from Alzheimer's patients have demonstrated that the redox modifications caused by oxidative stress inhibit the function of chaperones and the correct folding proteins, causing protein misfolding and ER stress [53]. In Alzheimer's pathology, β-protein has been reported to induce stress in the ER and change the morphology of the ER and also of the mitochondria. This results in the loss of the mitochondrial membrane potential and the consequent production of ROS [54].

2.9. Mitochondrial damage by oxidative stress

The mitochondria play a number of cell functions, such as ATP synthesis, calcium homeostasis, and processes of cell survival and death. Additionally, this organelle is the main source of endogenous ROS; therefore, it is constantly exposed to oxidative stress [55]. Several metabolic and mitochondrial abnormalities have been found in hippocampal neurons of patients with Alzheimer's. Mitochondria of AD patients show a reduction in size, DNA alterations, and mitochondrial proteins in vacuoles, suggesting mitochondrial degradation by autophagy [56]. Studies have also observed deficiencies in the production of antioxidant enzymes that play a protective role protecting the mitochondria from the damage caused by ROS; for example, there are the cytochrome oxidase complex IV, MnSOD, and uncoupling proteins [57].

2.10. Loss of regulation of inflammatory response

The immune defense of the central nervous system (CNS) is composed of a number of small cells known as microglia, astrocytes, and an effective blood-brain barrier [58]. The presence of an oxidative stress state causes the activation of the microglia and the astrocytes. As a result, inflammatory and neurotoxic factors are released increasing the levels of oxidative stress and causing a chronic neuroinflammatory response. Depending on its duration, the response may cause damage in the brain tissue [59]. Neurodegenerative diseases are characterized by a chronic dysregulation of the inflammatory response that involves glial alteration. This produces alterations in the neuronal metabolism, neuronal survival, and repair that progress to neuronal death and memory disturbances [4].

2.11. Oxidative stress state and dendritic spines

The chronic oxidative stress state causes alterations in dendritic spines. These alterations consist of a reduction in the size of the spines as well as a decrease in their number. This phenomenon is present in neurodegenerative diseases and in chronic diseases as alcoholism [60, 61]. An explanation of this histologic alteration found in the hippocampus of the patients is the loss of the existing regulation in calcium metabolism during oxidative stress state. There is an increase of extracellular Ca^{2+} entry, which tries to be regulated by the cells; they send Ca^{2+} to the ER or the mitochondria to avoid the alteration Ca^{2+}-dependent cell functions [62].

In addition, some studies have proposed a neuronal defense mechanism in which the cell tries to decrease the membrane surface exposed to free radicals, with the final purpose to try to control the balance in the intraneuronal medium [63]. All these changes affect the number of synapses and the metabolic interaction between astrocytes and neurons.

2.12. Oxidative stress state and neuron-glia interaction

The signaling and metabolic changes that occur in the presence of oxidative stress affect the interaction between neurons and astrocytes, and cause the activation of the microglia, inducing and maintaining the loss of regulation of the inflammatory response [64]. Among these alterations, we find the loss of regulation in neurotransmitter metabolism as glutamate, dopamine, as well as alterations in the metabolism of antioxidant systems like glutathione [65, 66]. On the other hand, the changes in the expression of inducible nitric oxide synthase and in the extracellular Ca^{2+} levels cause the release of proinflammatory cytokines as interleukin (IL)-1, IL-3, IL-6, interferon (IFN)-α, IFN-β, and tumor necrosis factor (TNF)-α by the astrocytes (**Figure 2**). This promotes the maintenance of the inflammatory response and the stimulation of the glia, creating a vicious cycle consisting of oxidative stress, cytokine release, inflammatory response, and increase of oxidative stress [67].

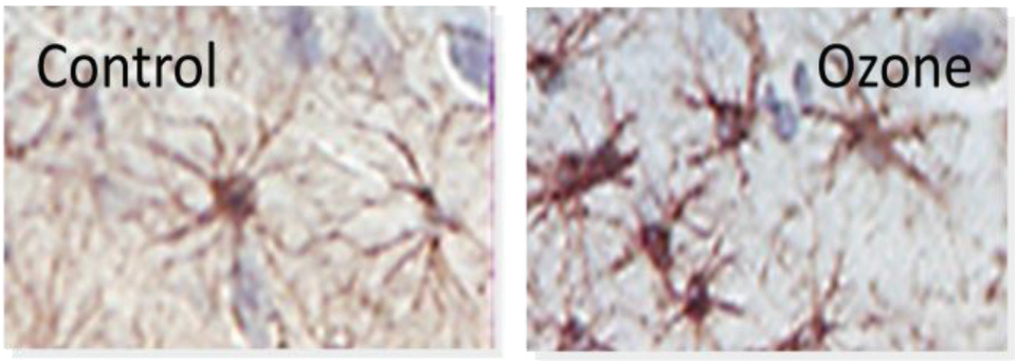

Figure 2. Microphotography that shows the chronic effect of oxidative stress in hippocampal astrocytes from rats exposed to low doses of ozone (40×). There are changes in the astrocytes in the samples from animals exposed to ozone.

2.13. Oxidative stress state and disturbance of the blood-brain barrier

The blood-brain barrier finely regulates the entry of substances into the brain. Among its functions is the capability of changing the affinity of the transporters according to the necessities of the nervous tissue [68]. This barrier is created by a close relationship between neurons, astrocytes, and endothelial cells; the microglia is involved as well [69]. The barrier creates a neurovascular unit that promotes neuronal homeostasis maintenance. Nevertheless, in neurodegenerative diseases and during inflammatory processes, this barrier is broken down and loses its selectivity [70]. We have proven that the blood-brain barrier is broken and there are changes in the morphology of the end feet of astrocytes in animal models of neurodegeneration caused by oxidative stress in the hippocampus of rats exposed to ozone [71]. Finally, this break is followed by endothelial cell edema, changes in the processes and in astrocytic

feet, and an increase of the proinflammatory factors. It promotes the exacerbation of the neurodegenerative process [72]. Oligomer production of β-amyloid increases oxidative damage of the blood-brain barrier, attracting astrocytes, glia, and activated microglia [73].

3. Oxidative stress and Alzheimer's disease

3.1. APP processing and β-amyloid formation

The break of the amyloid precursor protein (APP) has two phases: a nonamyloidogenic pathway and an amyloidogenic pathway. The amino acid 83 is cleaved by the α-secretase on the carboxyl-terminal, producing a long amino N-terminal ectodomain (sAPPα). The result of this process is the formation of C83, which is retained by the membrane to be cleaved by gamma secretase, creating short p3 fragments. The break down by α-secretase occurs within the β-amyloid region, preventing the formation of β-amyloid [74].

On the other hand, the amyloidogenic pathway is an alternative APP breakdown which leads to the creation of β-amyloids. This pathway is created by the β-secretase cleaving in the amino acid 99, allowing sAPPβ release in the extracellular space [75]. In consequence, the breakdown of this fragment between the 38 and 43 residues by the γ-secretase releases an intact Aβ peptide [76]. The complete β-amyloid peptide is 40 residues long ($A\beta_{40}$) and 10% is a 42-residue variant ($A\beta_{42}$). This variant is more hydrophobic and easily induces the formation of fibrils. It is also the largest form of this peptides prevailing the β-amyloid plaques [77].

There is a variety of assembly forms in which the β-amyloid peptide can be found. This peptide can carry out different physiological or pathological functions depending on the assembly pathway [78]. The β-amyloid can be deposited in specific brain regions forming amyloid plaques [79, 80].

3.2. Oxidative stress and alteration of the enzymes involved in the processing of APP

Among the different hypotheses explaining the possible causes intervening in the development of the disease, the participation of oxidative stress is nowadays widely accepted. Results obtained in our laboratory show that oxidative stress in healthy animals is per se capable of producing hyperphosphorylated tau protein and the formation of isoforms of β-amyloids 1-42 in hippocampal neurons of rats chronically exposes to low doses of ozone [81] (**Figure 3**).

The formation of senile plaques is due to intracellular and extracellular accumulation of insoluble β-amyloids in the brain. The β-amyloid peptide is generated by APP cleavage where the enzymes α, β, and γ secretases are involved as previously indicated [82]. Both the enzymes of the amyloidogenic pathway as the enzymes of the nonamyloidogenic pathway are altered by a chronic oxidative stress state. Experiments performed in our laboratory demonstrate that chronic oxidative stress, caused by exposure to low doses of ozone, is capable of inhibiting the enzymes involved in the nonamyloidogenic pathway. It also increases the enzymes in the amyloidogenic pathway in the hippocampus of rats which were exposed to this gas for 4 hours during 60 and 90 days (**Figures 4** and **5**).

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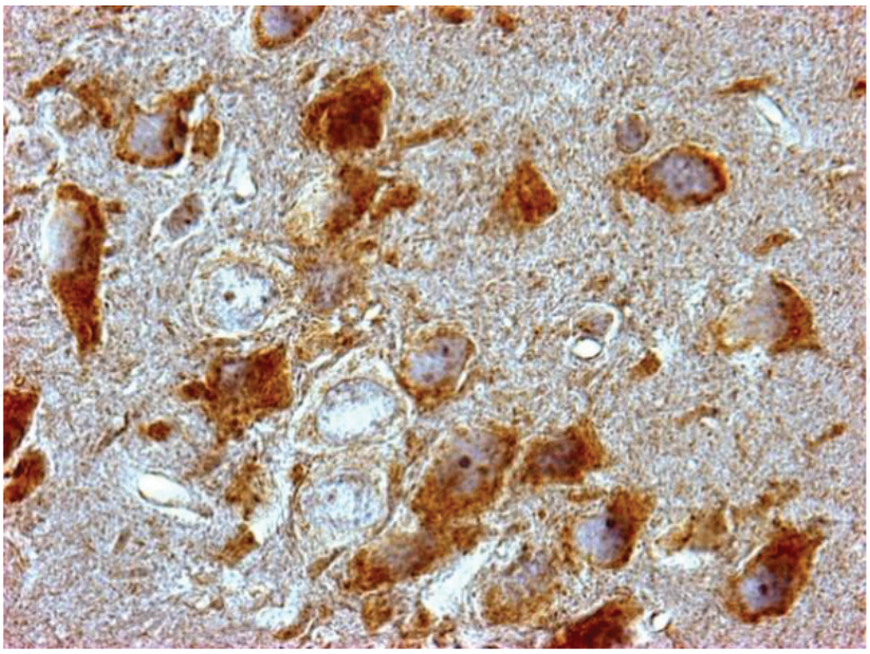

Figure 3. Micrography that shows the chronic effect of oxidative stress on the formation of β-amyloid 1-42 in rat hippocampus exposed to low doses of ozone for 90 days (100×). Note changes in intracellular accumulation of β-amyloid 1-42 in neurons of the dentate gyrus.

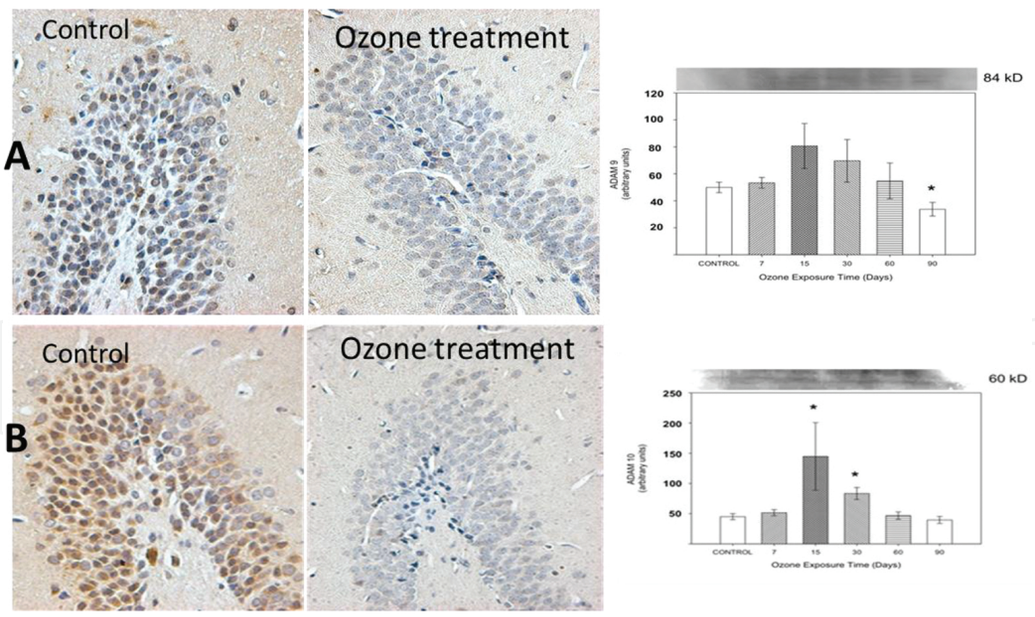

Figure 4. Micrography that shows the chronic effect of oxidative stress on the enzymes of the nonamyloidogenic pathway (A: ADAM 9; B: ADAM 10) in dentate gyrus of rat hippocampus exposed to low doses of ozone (40×). Note the decrease in immunoreactivity after 90 days of exposure to ozone compared to the control.

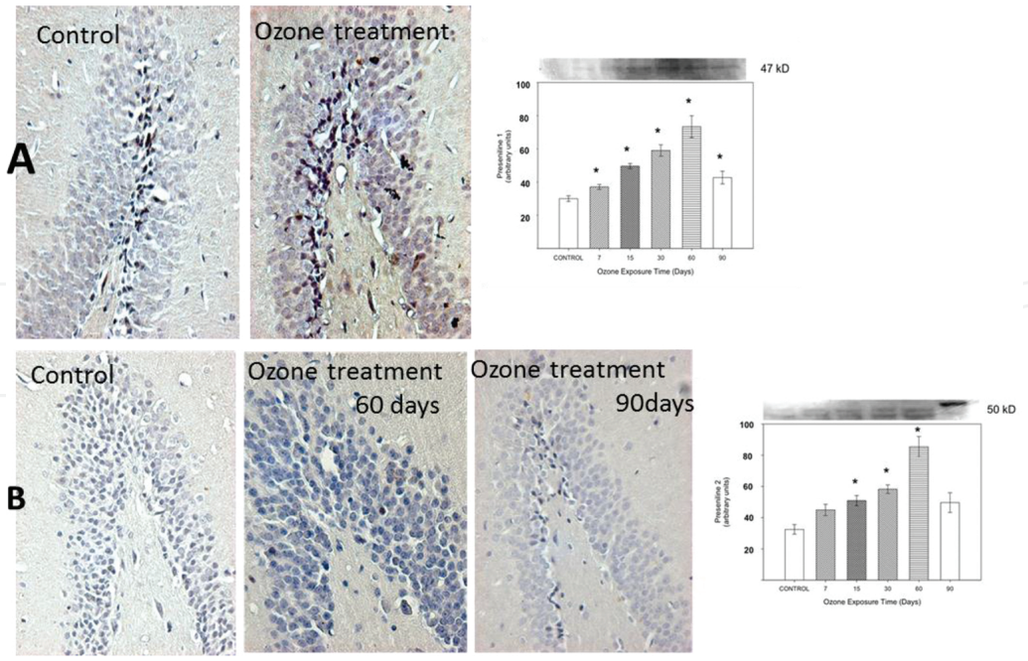

Figure 5. Micrography that shows the chronic effect of oxidative stress on the amyloidogenic pathway enzymes (A: presenilin 1; B: presenilin 2) in the dentate gyrus of rat hippocampus exposed to low doses of ozone (40×). Note the increase in immunoreactivity at 90 days for presenilin 1 and presenilin 2 to 60 days in the brains of animals exposed to ozone compared to the control.

The β-amyloid accumulation in specific compartments of the neuron causes an energy deficit and alterations in protein folding [83, 84]. For its part, the intracellular increase of these oligomers causes the inhibition of the proteasome activity, lowering the possibility of processing misfolded proteins and causing their accumulation buildup within the cell [85].

The β-amyloid accumulation attracts immune system cells such as astrocytes, activated microglia, and macrophages, among others. Glial cells maintain the loss of regulation of the inflammatory response, the inflammation, and the oxidative stress state, creating a vicious cycle that is maintained in time [86].

When the levels of the intracellular β-amyloid peptide decrease, the internalization of APP is induced. The internalization is mediated by the low density lipoprotein receptor-related protein 1B (LRP1B), one of the members of the LDL family. This receptor usually binds APP to the plasmatic membrane to prevent the internalization of the β-amyloid peptide, reducing its production [87]. The failure of these mechanisms by the effect of oxidative stress and the hyperphosphorylation of tau protein induced a disturbance in the formation of microtubules, producing neurofibrillary tangles [88]. Furthermore, tau protein associates with β-amyloids that might be involved in the internalization of the extracellular protein into the neurons. This produces and externalizes the insoluble isoform of β-amyloid [89]. During this phase, the synthesis of soluble β-amyloid is decreased while the synthesis of misfolded insoluble β-amyloids is increased. It forms part of the insoluble β-amyloid plaques [90].

Finally, our laboratory has developed a noninvasive model of oxidative stress using the exposure to low doses of ozone to that effect. Using this model, we have proven that oxidative

stress per se is capable of producing progressive neurodegeneration in the hippocampus together with the formation of insoluble β-amyloid 1-42 and the accumulation of such peptides.

4. Conclusions

The loss of redox homeostasis accelerates ageing and plays a fundamental role in the pathogeny and development of Alzheimer's disease. It alters the cell signaling mechanisms of an important number of metabolic pathways, promotes epigenetic alterations, and alters the posttranslational mechanisms. Finally, the chronic alteration of the redox balance induces the misfolding of proteins by oxidative stress in ER, cholesterol oxidation, and alterations in insulin receptors that lead to changes in neuronal metabolism and survival.

We can infer that Alzheimer's disease is the final manifestation of a series of oxidative alterations of the metabolism. There is a slow involvement of different biomolecules during the development of the disease. The loss of redox balance plays a crucial role in the formation of hyperphosphorylated tau protein, insoluble β-amyloids, and the loss of regulation of the immune system.

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