

SYSTEMIC OXIDATIVE STRESS: A KEY POINT IN NEURODEGENERATION – A REVIEW

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Abstract: Systemic oxidative stress (SOS) has an important role in the mechanisms activation of neuronal death, involved in the neurodegenerative disease (ND) etiology. Brain is susceptible to oxidative stress injuries due to its high energy and metabolic request, therefore minimal imbalances of the redox state, as occurs in mitochondrial dysfunction, favour tissue injury and neuroinflammatory mechanisms activation. ND affect around the world about a billion people, without distinction of sex, educational level and economic status. Public measures generation that prevent ND from the SOS are possible promising therapeutic targets that could reduce the ND incidence. We discuss here the effects and mechanisms of SOS derived neurodegeneration, as well as the neuroinflammation repercussions for some cerebral structures.

Key words: Oxidative stress, inflammation, neurodegenerative diseases, free radicals, antioxidants.

Neurodegenerative disease - A central matter

Neurodegenerative diseases (NDs) form a heterogeneous group of diseases that mainly have their point of injury in the nervous system (NS). They are characterised by the progressive loss of neurons, known as neurodegeneration, in regions that compromise NS functions (1).

According to the World Health Organization (WHO) report, ND affects around a billion people worldwide. The report, “Neurological Disorders: Public health challenges” cites the global prevalence of ND to be 50 million cases of epilepsy and 24 million of Alzheimer’s and other dementias. Neurological disorders affect people from all countries irrespective of sex, educational level and economic status. The WHO advocates that neurological care be integrated into primary health care in order to prevent ND through strategies that can also directly affect metabolic disturbance aspects (2, 3).

NDs share a common binomial with other diseases such as diabetes, cardiovascular disease and adiposity-based chronic disease (obesity). The oxidative stress and chronic inflammation binomial (OS-I) is much more than the consequence of oxidative-reductive alterations that lead to neuronal death (4, 5). OS-I is an important aetiological factor in the development of metabolic disease (6), that lately has gained greater prominence in the study of ND, to elucidate the various mechanisms involved between alterations in the cellular redox state and the injury to NS structural components (7). However, many questions remain to be resolved; for example: Is oxidative stress the cause or a consequence of the development of ND? What are the implications of systemic oxidative stress (SOS) in the oxidative alterations development at the NS level? Is chronic oxidative stress an early ND trigger? In the present review, we discuss the effects and mechanisms of SOS-derived neurodegeneration, as well as the repercussions of neuroinflammation for some NS structures.

An updated context of oxidative stress based on the problems of the 21st century

The first studies of oxidative stress were reported in 1956 by Dr. Harman, who was the first to describe ageing as a phenomenon characterised by the progressive decline of cellular function and what is known as his oxidative stress theory (or the involvement of free radicals), describing the circumstances under which cells age and die (8). In recent decades, research into oxidative stress has increased, associating it with the development of metabolic disorders such as adiposity-based chronic disease (ABCD) (9), diabetes (10), cardiovascular diseases (CVD) (11), cancer (12) and recently, ND (13).

Society has undergone great economic, political and sociocultural changes that have influenced people’s lifestyles (14). People live in faster societies, with less time to consume fresh and natural foods, with greater work stress and economic crises that compromise the nutritional quality of their food, favouring the consumption of high ultra-processed products (UPPs) (15).

Twenty-first century society changes quickly and unpredictably. Currently, people live in an uncertain society, experiencing change and excess; these characteristics are also reflected in the attitudes to health systems, leading to important implications in the development of SOS, associated with the current incidence of chronic metabolic diseases (16). This is a reflection of the change in eating guidelines, regarding diets such as those high in simple carbohydrates (DHSCs) and in saturated fatty acids (DHSFs), characteristics of the Western diet (15). Food consumption guidelines play an important role in the increase in the levels of systemic pro-oxidants and inflammatory mediators, which result in neuroinflammatory responses in the central nervous system (CNS) structures such as the hypothalamus, choroid plexus, cerebellum, cerebral

cortex and hippocampus (17).

Mitochondrial dysfunction: Key point kick-off from systemic oxidative stress

Oxygen is a vital element for the correct every human operation being. Cell uses oxygen in oxidative-reductive reactions, in order to obtain energy and intermediate metabolites necessary for its growth, development, survival, homeostasis and adaptability (18). Specifically, the mitochondrion is the central subcellular organelle in the process of internal respiration (oxidative-reductive reactions) where the complete nutrients oxidation such as glucose and fatty acids is carried out in the intermediate metabolites production: ATP, H₂O y CO₂ (19).

Usually, mitochondria use 95 to 98% of O₂ get into oxidative processes. Another 2% of O₂ reacts with H₂O molecules to produce hydrogen peroxide (H₂O₂) or other species (O₂⁻, OH⁻), called reactive oxygen species (ROS) (20, 21). Several factors are related to the exacerbated ROS production, among them the diet quality. DHSC and DHSF they correlate with the intracellular increase pro-oxidant substances. Initially, skeletal muscle and adipose tissue are two tissues involved in oxidative-reductive alterations, in response to an increase in intracellular glucose concentrations due to changes in the diet quality. The intracellular increase glucose leads to a greater substrate amount for oxidative metabolism enzymes.

As the substrate concentration increases, the initial enzymes velocity increases to a saturation point (22). The enzymes saturation involved in oxidative processes, conditions the decrease in the physiological O₂ use, producing an increase in free O₂, and ROS overproduction (21, 18), decrease in oxidative phosphorylation and decrease in ATP production. These alterations in the oxidative processes, result in a higher ROS production and lower ATP. These mitochondrial perturbations oxide-reductive processes are known as mitochondrial dysfunction (23).

Disturbances to the redox state in the mitochondria are considered the main triggering OS-I factor, a situation that compromises oxide-reductive cell functions, after the exacerbated ROS increase and free radicals (FR) and lower antioxidant production substances. ROS and FR, are atoms or atoms groups with an unpaired electron, such compounds are characterised by sequestering electrons from electrochemically stable molecules, such as proteins, lipids and nucleic acids (24). The ability to sequester electrons depends on the atom electronegativity; because oxygen and nitrogen are highly electronegative elements, ROS and reactive nitrogen species (RNS) are produced more easily, respectively. Reactive species are produced as part of everyday physiological processes and have important roles in cell signalling, gene transcription and immune response (25). However, the FR overproduction, generates oxidative damage on cellular structures (26).

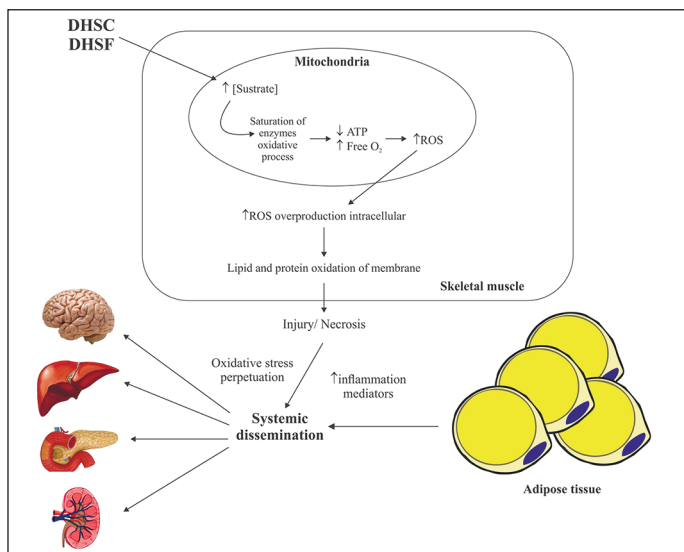
ROS accumulation in mitochondrial matrix, induces

oxidation lipids and proteins membrane, which contribute to mitochondrial dysfunction (21). Additionally, disturbances in mitochondrial DNA due to oxidation by ROS, is correlated with a lower genes expression responsible for coding mitochondrial protection proteins against oxidative stress. Although the mechanisms involved are still unclear, up to 30 mutations in mitochondrial DNA have been identified, related to the pro-oxidative environment (27). DNA oxidation and mitochondrial membranes, with their subsequent fragmentation, implies an irreversible cellular lesion. Finally, mitochondria death and the decrease in ATP production, activate cell death signals that trigger proinflammatory processes (26).

Oxidative stress perpetuation, leads to a chronic state that propagation to other tissues. ROS and RNS in blood are capable of triggering proinflammatory and oxidative processes in organs such as liver (28), kidney (29), enterocyte (30), endocrine glands (6), encephalon (31), among others, associated with the metabolic diseases development (Figure 1). For the purposes of this review, the following sections will focus on the SOS effects and its affections on the NS, as a potential trigger of ND.

Figure 1

Systemic dissemination by mitochondrial dysfunction



Blood-Brain barriers (BBB) alteration due to the SOS

Dissemination of pro-oxidant compounds in the blood and inflammatory mechanisms activation compromises CNS functions through different communication channels, such as the vagus nerve, the choroid plexus and the BBB (32). NS has protection from the pro-oxidants accumulation in blood, through the BBB, therefore, its disruption implies the components filtration that injury the NS (33). BBB is a physical barrier located between blood vessels and brain tissue, which selectively limits the access of molecules to protect the brain from any pathogen type or toxic substance. It is an active structure that reacts to stimuli by modifying its permeability and

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uptake capacities (34).

SOS favours a chronic oxidative environment that leads to changes related to the cells epigenetics of the neurovascular unit (NVU) that alter the BBB integrity (33). NVU includes endothelial cells, capillaries and pericytes surrounded by basal lamina, which are surrounded by astrocytes very close to the neurons and microglia. So, BBB expresses a large ion number channels and transporters, has a low pinocytosis rate and tight junction proteins (TJ) intercellular, such as occludin, claudins and cell adhesion molecules, which limit paracellular permeability (34).

As a protection, endothelial cells of the BBB have a high antioxidant activity rate. They have significant reduced glutathione (GSH) amounts, glutathione peroxidase (Gpx), glutathione reductase and catalase (CAT), compared to the brain rest. Specifically, GSH plays a crucial role in the BBB integrity, reducing the damage caused by ROS and FR (33). However, antioxidant activity is compromised in a chronic oxidation environment (35), as is the DHSC and DHSF case.

Among the most widely studied factors causing the BBB disruption are the DHSC and DHSF (36, 37). ROS contributes to brain injury by reacting with proteins, lipids and nucleic acids, as well as by activating a number of signalling pathways sensitive to redox. ROS overproduction affects the BBB permeability by a mechanisms variety, including the modulation of binding proteins, as is the case with occludin and claudin (38).

Occludin is a transmembrane protein present in the oligomers form in the plasma membrane of the BBB. Multiple domains of occludin regulate the solutes diffusion through binding proteins (39). Occludin oligomers are held together covalently by disulfide bonds, sensitive to ROS oxidation. Changes in the structure of the occludin oligomers, leads to a lower capacity of the binding protein complexes to limit the paracellular diffusion of the blood molecules to the brain (40).

A chronic oxidation environment is associated with lower genes expression cytoskeletal proteins, chaperones, enzymes, transport-related proteins and regulators for transcriptional and translational of brain microvessel cells, causing changes in the regulation of the peptides and substrates transport that cross the BBB. DHSC and DHSF it is associated with lower mRNA expression of tight binding proteins, particularly claudin-5 and -12, in the choroid plexus and BBB (41).

All the organism cell, including NVU, present a defence mechanism against the OS called adaptive response (AR) (42). In response to the OS, the cell expresses antioxidant enzymes genes, activating the transcription factor Nrf2, at the same time that it inhibits enzymes genes involved in the ROS production, such as NADPH oxidase, anti-inflammatory mediators increase, proteasome activity and other transcription factors involved in mitochondrial biogenesis (43).

Although the SNC has a protective defence mechanism against the OS, in addition to the BBB (33), the generalised and chronic oxidative environment is a factor that leads to the

loss of the AR (24). Lower genes expression involved in the NVU integrity, causes a hypometabolic state that influences the oxidative processes of the cells that make BBB (37). The mitochondrial dysfunction triggered, favours cellular injury that culminate in endothelial cell necrosis and loss of BBB integrity.

Chronic oxidative stress and neurodegeneration

With a 2 kg weight (3% of body composition) the NS is one of the smallest and most complex organs of the body. It consists of an intricate, specialised and highly organised network of cells called neurons and glial cells. The NS is subdivided into CNS, consisting of encephalon and spinal cord, and the peripheral nervous system (PNS), which includes all nerve tissues located in the periphery. The brain is the main constituent organ of the CNS, whose cognitive function involves the participation of cell networks that include neurons, one of the most important NS cell populations (44).

Neurons are the main functional units of the CNS and have the ability to communicate with each other quickly and efficiently through electrical or chemical signals that are translated as action potentials. Structurally, they are composed of a cell body (soma) where the nucleus is located and where several extensions are projected (appendices or protuberances), which include many short branching extensions, known as dendrites and a separate extension that is usually longer than dendrites, known as axon (45).

Unlike other cells, neurons use a lot of oxygen (20% of the O₂ that enters the organism), so they have a high mitochondrial activity rate that allows them to cover high ATP demands; however, the above is a crucial point also for increased ROS production. Especially, neurons are more sensitive to the accumulation and damage induced by ROS (5).

Not all nerve cells produce action potentials. Glial cells differ from neurons, since they do not have synaptic contacts and have the ability to divide throughout life. The main glial cells functions are: 1) Maintain an ionic medium in nerve cells; 2) Modulate the propagation speed of nerve signals; 3) Modulate the synaptic action by controlling the neurotransmitters uptake; 4) Provide a foundation for neural development; and 5) Contribute (or prevent, in some cases) the survival of a neuronal lesion (46). The glial cells are together with the NVU, responsible for the BBB integrity and neuronal metabolism, by preventing / responding to nerve tissue injury (47).

Microglia constitute part of the macrophages and constitute between 5 and 10% of the neuronal cell population (47). Under basal conditions, it is at rest; however, in response to NS injury, the microglia becomes polarised (morphological transformation of an inactive branched state to an active phagocytic amiboide) and triggers mechanisms that promote neurotoxic activities, including the ROS overproduction, RNS, chemokines and proinflammatory cytokines. The above is called microgliosis, whose main characteristic is an increase in the microglias

number activated at the site of the lesion, which leads to a complex cascade of physiological acute inflammation responses (48, 49).

The chronic state of OS in the organism, systemic ROS dissemination and BBB disruption, causes a chronic microgliosis response that promotes a chronic state of inflammation. Activation of the microglia remains until it becomes chronic, which leads to an imbalance in the inflammatory response, generating a neuroinflammation cycle and tissue damage (46).

Neuroinflammation is the set of mechanisms and physiopathological phenomena mediated by alterations in the glial cell morphology. It is a reactive state of the immunological component of the CNS (50). The damage responsible for triggering neuroinflammation can be: a) Physical, such as trauma; b) Biological, such as bacterial or parasitic infections in NS; or c) Chemical, as is the case of an exacerbated ROS production, FR, and RNS, present in the SOS (19).

In response to the damage and the consequent microglial activation, involved proinflammatory molecules that mediate the response at the damage site. IL1 β induces the expression of the inducible nitric oxide synthase gene (iNOS), responsible for triggering the nitric oxide (NO-) release, on glial cells and cause nitrosative stress. An exacerbated RNS production, as it happens in the chronic neuroinflammatory response, increases the oxidation of cell membrane lipids (48).

Likewise, astrogliosis (activation of the inflammatory response by astrocytes), increases the number and size of the fibrillary acid protein (FAP) of the glia, cytoskeletal protein that contributes to hypertrophy and hyperplasia of astrocytes. Active astrocytes produce a molecules variety, which are involved in the initiation, progression and regulation of the inflammatory response. In addition to the pro and anti-inflammatory cytokines production, there is a greater expression of the genes of the cyclooxygenase – 2 (COX-2) enzymes e iNOS, as well as higher RNS production. Neuroinflammatory response, initially triggered by ROS and FR, contributes to oxidative stress in the CNS, generating a perpetuated state between neuroinflammation and chronic oxidative stress (51).

OS plays a critical role in the neuronal activation death mechanisms, implicated in the several aetiology ND (52). Brain is susceptible to EO lesions due to its high energy use and metabolic demand, therefore minimal imbalances of the redox state, as occurs in mitochondrial dysfunction, favour tissue injury, damage and neuroinflammatory mechanisms activation (53).

OS perpetuation, produces the genes activation involved in the recovery and cell death, one of the most studied is the FOXO transcription factors. The FOXO transcription factors have a central role in oxidative stress-induced neuronal cell death. FOXO promotes neuronal apoptosis in response to oxidative stress through inducing the expression of pro-apoptotic downstream genes including Bim and FasL (54). Likewise, exacerbated ROS production intracellular

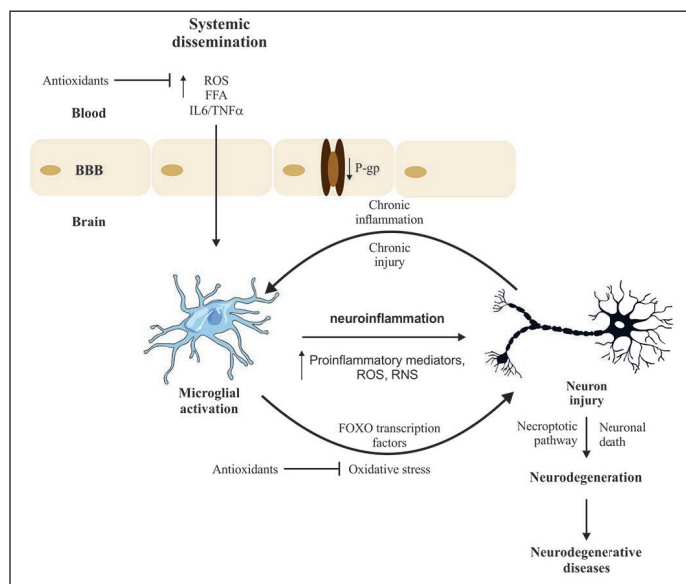
and DNA damage induces the expression of the p53 gene, activating the Bcl2 pro-apoptotic protein family, Bax and Bad permeabilisation of the mitochondrial outer membrane with translocation and release of cytochrome C that forms a complex with apoptotic protease activating factor 1 (Apaf-1). Result is the 9 caspase activation, leading to a proteolytic caspase activation cascade 3 and 7, and execution of the cell death process, as well as changes in the plasma membrane (blistering and phosphatidyl-serine exposure on the cell surface which is a signal that stimulates cellular phagocytosis by macrophages / microglia) that culminates in the condensation and nuclear chromatin fragmentation (55, 56).

Increase in ROS concentrations in the neuron, induces a rapid increase in intracellular Ca⁺², from: 1) extracellular spaces, after the rupture of the membrane and, 2) release of the endoplasmic reticulum, causing cytochrome C translocation from the mitochondrial outer membrane to the cytosol, triggering cell death signals (56). Likewise, another mechanism involved in cell death, is the BBB disruption, which dissipates the ROS passage and proinflammatory cytokines to NS. Disengagement microgliosis, increases the inflammation mediators production, ROS and RNS, causing cell death signs, by recognising the FAS receptor or cell death receptor and TNF receptor 1 (TNFR1), activating the necroptotic pathway, also related to the ND pathogenesis (Figure 2) (57).

Unlike other organism cells, neurons have a low regenerative activity, apoptotic pathway is highly restricted, to allow neurons to survive during the life of an organism (58). Regions such as the adult hippocampus do not present a neurogenesis in the dentate gyrus, associated with the early cognitive decline of the ND (59).

Figure 2

Systemic oxidative stress effect on the neurodegenerative disease development



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Therapeutic perspectives

Advances in medical and biotechnology sciences have redirected the way nutrition is done. Currently the implementation of a feed from the bioactive compounds present in them, whose biological activity has shown beneficial effects on the SOS biochemical-metabolic alterations (60- 62).

The antioxidants use to mitigate the OS alterations, it is an alternative in the modulation of the oxidative environment. An antioxidant is any substance that is present at low concentrations with respect to those of an oxidisable substrate (biomolecule), retards or prevents the oxidation of the substrate (63). Currently, a role of antioxidants is proposed as neuroprotective agents in ND. Polyphenols such as quercetin, catechin and resveratrol that have exhibited neuroprotective capacity in several animal models with neurological disorder (64). Epidemiological research support the potential polyphenols use in the diet, on better neuronal health (65). The proposed mechanisms include the blocking of specific enzymes that generate FR, metals chelation and neutralising ROS, anti-inflammatory effects and microglia inhibition recruitment (66).

Fruits and beverages such as tea, red wine, cocoa and coffee are the main polyphenols dietary sources (65). Its neuroprotective effects are correlated through the potential to protect neurons against lesions induced by neurotoxins, the ability to suppress neuroinflammation and the potential to promote memory, learning and cognitive function (67). Recent evidence suggests that its beneficial effects involve decreases in OS signalling and modulation of gene expression of antioxidant enzymes, neurotrophic factors and cytoprotective protein (68).

Other compounds of interest such as caffeine (69), Ginkgo biloba (70), α -tocopherol (71) and curcumin (72), they have also shown important protective activities and suggest a potential use in the ND treatment. The therapeutic strategies development based on the potential antioxidant and anti-inflammatory effect of food are useful for modulating the oxidative environment and mitigating OS alterations and inflammation (73).

Conclusion

SOS it is a complex reversible entity, whose chronicity can lead to other systemic disturbances such as neurodegeneration. Its early detection would be a window of opportunity for the ND prevention. The use of dietary antioxidants is important to mitigate the biochemical-metabolic alterations product of the oxidative environment generated by the OS. The search for new strategies of functional nutrition, based on the functional potential of antioxidants are allies in the prevention of diseases with an oxidative base.

Conflict of Interest: The authors declare that they have no conflict of interest.

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