Mechanisms of Ageing and Development 189 (2020) 111250

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Redox modifications in synaptic components as biomarkers of cognitive status, in brain aging and disease

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ARTICLE INFO

Keywords:
Brain aging
Oxidative stress
Redox modifications
microRNAs
Alzheimer´s disease

ABSTRACT

Aging is a natural process that includes several changes that gradually make organisms degenerate and die. Harman's theory proposes that aging is a consequence of the progressive accumulation of oxidative modifications mediated by reactive oxygen/nitrogen species, which plays an essential role in the development and progression of many neurodegenerative diseases. This review will focus on how abnormal redox modifications induced by age impair the functionality of neuronal redox-sensitive proteins involved in axonal elongation and guidance, synaptic plasticity, and intercellular communication. We will discuss post-transcriptional regulation of gene expression by microRNAs as a mechanism that controls the neuronal redox state. Finally, we will discuss how some brain-permeant antioxidants from the diet have a beneficial effect on cognition. Taken together, the evidence revised here indicates that oxidative-driven modifications of specific proteins and changes in microRNA expression may be useful biomarkers for aging and neurodegenerative diseases. Also, some specific antioxidant therapies have undoubtedly beneficial neuroprotective effects when administered in the correct doses, in the ideal formulation combination, and during the appropriate therapeutic window. The use of some antioxidants is, therefore, still poorly explored for the treatment of neurodegenerative diseases such as Alzheimer's disease.

1. Introduction

Aging is a functional decline in multiple physiological and cellular functions that progresses throughout life, increasing susceptibility to disease (Singh and Newman, 2011). In the 1950s, Harman outlined a "theory of aging by free radicals," proposing that aerobic organisms live in the continuous presence of free radicals, mostly reactive oxygen species (ROS) that damage their cell macromolecules progressively during life (Harman, 1956). Like other aging theories, it fails to explain the entire aging process (Van Raamsdonk and Hekimi, 2012), as it does not establish a causal link between ROS and aging. Therefore, a more unified and integrated vision of the diverse approaches and existing theories (Lopez-Otin et al., 2013) is necessary. Regarding ROS, a revised version of this theory argues that abnormally high levels of ROS in aging may act as stressors, leading to functional alterations, diseases, and ultimately death (Hagen, 2003; Pomatto and Davies, 2018). Such revisited ideas have particular relevance at the brain level, owing to its high oxygen consumption that reaches up to 20 % of the whole body's

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https://doi.org/10.1016/j.mad.2020.111250
Received 9 December 2019; Received in revised form 5 March 2020; Accepted 10 April 2020
Available online 17 May 2020

consumption (Jain et al., 2010).

On the other hand, low antioxidant capacity and a high presence of heavy metals associates with the presence of some polyunsaturated fatty acids (Perkins et al., 1999; Perrig et al., 1997; Rinaldi et al., 2003). These molecules favor specific oxidative reactions, leading to the formation of both conjugated dienes and lipid hydroperoxides, increasing the vulnerability of the brain to the effects of oxidative stress and aging. Oxidative stress is a risk factor for the development and progression of many neurodegenerative diseases (ND), such as Alzheimer's Disease (AD), among other central nervous system aging-associated disorders (Butterfield and Perluigi, 2017; Calabrese et al., 2009; Texel and Mattson, 2011).

In this context, the idea of eliminating ROS to solve the problem is intuitive, but displacements from the normal cellular redox state, also termed oxidative eustress, to a reduced state, is also detrimental. The explanation for this is that ROS are also fundamental in redox signaling as second messengers, undergoing a cross-talk with Ca^{2+}-mediated signaling and with other critical intracellular pathways (Hidalgo and Nunez, 2007). Hence the progressive loss in neuronal function, along with the increased prevalence of diseases, could result from the progressive loss of redox signaling, which would be present in early stages of aging and of certain ND such as AD, before the detection of oxidative damage (Kumar et al., 2018; Sbodio et al., 2019).

There are several reviews in the literature covering the different intracellular ROS sources and the primary antioxidant mechanisms available in the nervous system (Droge, 2002; Finkel and Holbrook, 2000; Nunez and Hidalgo, 2019; Pomatto and Davies, 2018; Sies et al., 2017; Valko et al., 2007). This review will focus on how redox modifications alter the functionality of neuronal redox-sensitive proteins that are critical in neuronal pathways, which lead to altered physiological responses associated with axonal elongation and guidance, neuronal plasticity, learning, and memory. We will also discuss how epigenetic regulation is crucial in controlling redox signaling, focusing on post-transcriptional regulation mediated by microRNAs (miRNAs) as a mechanism that quickly and effectively modulates the levels of both antioxidant and ROS-generating enzymes. Finally, we will highlight the effect of certain brain-permeant antioxidants from the diet, which have a probed beneficial effect on human cognition.

2. ROS and enzymatic and non-enzymatic antioxidants

ROS, such as superoxide anion radical ($O_2^{\bullet -}$), peroxynitrite (ONOO-), and hydroxyl radical ($OH^{\bullet -}$) are unstable and short-lived species. In contrast, hydrogen peroxide (H_2O_2) and nitric oxide (NO) show a higher half-life that makes them prone to act as signaling molecules. In brief, ROS generation occurs by either exogenous sources (as UV radiation or some drugs) or endogenous, including NADPH oxidase complex (NOX) located on the plasma membrane, mitochondrial complexes III and I on the electron transport chain. Also, monoamine oxidase (MAO) on the outer mitochondrial membrane and cyclooxygenase (COX) located in the endoplasmic reticulum (ER) membrane are other sources of ROS (Fig. 1). On the other hand, nitric oxide synthase (NOS) cytosolic enzyme is the primary source of nitric oxide. In neurons, nNOS (neuronal NOS) interacts with the scaffold protein PSD-95 (Fig. 1), allowing their association with synaptic membranes and neurotransmitter receptors (Finkel and Holbrook, 2000; Valko et al., 2007).

Also, iron ions (Fe^{2+}, Fe^{3+}) participate in a series of redox reactions that favor ROS production (Fig. 1). Among them, the Fenton reaction is pivotal because it converts H_2O_2, a product of mitochondrial oxidative phosphorylation, into a highly toxic hydroxyl free radical, the hydroxyl radical (•OH). The Fenton reaction can be considered the toxic moiety of the Haber-Weiss reaction, which is the whole reaction that combines Fenton reaction to the reduction of Fe^{3+} by $O_2^{\bullet -}$, to produce Fe^{2+} and molecular oxygen (Kell, 2009). These iron-mediated reactions, therefore, may lead to the generation of harmful concentrations of free radicals, triggering the oxidative damage in various cellular components (Nunez and Hidalgo, 2019).

Organisms have developed diverse enzymatic and chemical antioxidant systems to neutralize ROS damaging effects (Finkel and Holbrook, 2000; Valko et al., 2007). Superoxide dismutase, catalase, and glutathione peroxidase, thioredoxins, and peroxiredoxins are among the neuronal enzymatic antioxidants that counteract the abnormal accumulation of ROS. The non-enzymatic antioxidant system includes low molecular weight compounds such as glutathione (GSH), α-tocopherol, ascorbic acid, and β-carotene. These molecules neutralize oxidant species, either suppressing or breaking chain reactions, similar to other antioxidant molecules such as bilirubin and uric acid (Mironczuk-Chodakowska et al., 2018).

On the other hand, there is a wide variety of antioxidants derived from the diet, such as phenolic acids, flavonoids, isoflavones, flavones, anthocyanins, and coumarins. Mounting evidence has pointed these molecules as potentially useful in the treatment of oxidative stress. Although the antioxidant structures are out of the scope of this review, we will discuss some proposed mechanisms involved in neuroprotection mediated by antioxidants with proven effects on the human nervous system and cognition (Pisoschi and Pop, 2015).

3. Redox regulation at the protein level

In terms of its physiological relevance, the covalent and reversible redox modifications of proteins are comparable to other post-translational modifications such as phosphorylation, glycosylation, or methylation. There are several redox-sensitive proteins, such as Ca^{2+} channels, receptors, protein kinases, protein phosphatases, and transcription factors that respond to oxidative modification by H_2O_2 (Droge, 2002). Given their potential capacity to cause excessive damage to neurons (Sies, 2017), the function as signaling messengers exerted by H_2O_2 presupposes the necessity of their quick elimination, to which several antioxidant mechanisms are required (Paul et al., 2018). For instance, H_2O_2 interacts with cysteine residues in redox-sensitive proteins, inducing rapid oxidation and formation of disulfide bonds between cysteines. The reversion of this process is possible and occurs when disulfide bonds are broken by reducing agents or by enzymes that depend on GSH or NOX (Cai and Yan, 2013).

On the other hand, NO is a free radical synthesized by NOS that induces S-nitrosylation of the thiol group in cysteine residues (Shahani and Sawa, 2011). Depending on the oxidative stress level, NO may coexist with other reactive species such as $O_2^{\bullet -}$. This coexistence, in turn, causes the production of ONOO−, which is a highly reactive free radical that, in the presence of CO_2, will nitrate proteins. ONOO− in its acid form decomposes rapidly in other nitrogenous species, generating 3-nitrotyrosine (Butterfield and Kanski, 2001; Calabrese et al., 2007).

The varying oxidation levels of the thiol group in cysteines modify the activity of proteins in different ways, either at their catalytic sites, binding domain, protein-protein interactions or protein stability (Anastasiou et al., 2011; Dotsey et al., 2015; Guo et al., 2010; Lee et al., 2013; Paulsen et al., 2011; Sobotta et al., 2015). All of the above have a substantial impact on protein function and redox-dependent cellular processes.

4. Neuronal redox signaling

H_2O_2 can act cellular messenger in long-term potentiation (LTP) of hippocampal synapses (Hidalgo et al., 2007; Knapp and Klann, 2002; Munoz et al., 2011). LTP is a well-studied type of synaptic plasticity (Boric et al., 2008; Castillo, 2012; Munoz et al., 2011) because it shares many molecular mechanisms with the memory process (Kandel and Pittenger, 2003).

At neuronal level, oxidative damage related to age (Kumar et al., 2018; Sbodio et al., 2019) strongly impairs the synaptic components involved in neuronal plasticity (Bodhinathan et al., 2010a,b; Arias-Cavieres et al., 2017; Muñoz et al., 2016), cytoskeletal dynamics

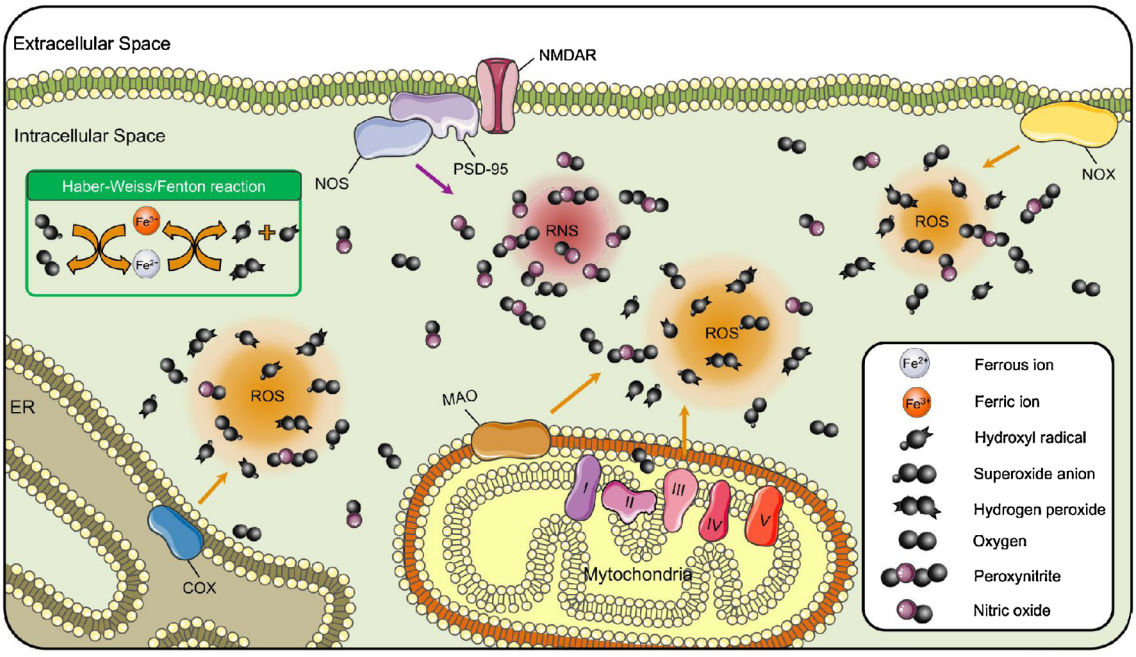

Fig. 1. Endogenous sources of oxygen and nitrogen reactive species. Reactive oxygen species (ROS) such as superoxide anion radical, hydrogen peroxide and hydroxyl radical, and reactive nitrogen species (RNS) such as nitric oxide and peroxynitrite anion, are molecules endogenously generated in part enzymatically from the reduction of oxygen to water, or directly through chemical reactions such as Fenton and Haber-Weiss reactions. In Fenton reaction, ferrous ion (Fe2 +) reacts with hydrogen peroxide to give ferric ion (Fe3 +) and hydroxyl radical. In close association with this reaction, in the presence of iron, hydroxyl radicals can be produced from hydrogen peroxide and superoxide anion by Haber-Weiss reaction. Enzymatic ROS production includes plasma membrane, mitochondrial, endoplasmic reticulum, and cytosolic located proteins. In neurons, neuronal NOS (nNOS), an enzymatic source of NO, interacts with the scaffold protein PSD-95, allowing their association with synaptic membranes and neurotransmitter receptors.

(Wilson and Gonzalez-Billault, 2015) and cellular communication (Quintanilla et al., 2012).

Some types of hippocampal plasticity affected with age (Arias-Cavieres et al., 2017; Boric et al., 2006) are triggered when glutamate released from the presynaptic terminal activates amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPAR) and N-methyl-D-Aspartate (NMDAR) receptors (Fig. 2). In particular, NMDAR activation allows Ca^{2+} influx to the postsynaptic terminal. Other proteins, such as voltage-dependent Ca^{2+} channels (VDCCs), connexin and pannexin channels, contribute to Ca^{2+} influx (Emptage et al., 1999; Saez et al., 2003). In neurons, Ca^{2+} influx through voltage-dependent Ca^{2+} channels or neurotransmitter receptors mobilizes Ca^{2+} from the endoplasmic reticulum (ER) to amplify Ca^{2+} signals either through the activation of inositol 1, 4, 5-trisphosphate (IP3) receptors (IP3R) or of ryanodine receptors (RyR) (Berridge, 2002), which mediate a conserved mechanism of Ca^{2+}-induced Ca^{2+} release (CICR) (Roderick et al., 2003). Notably, the contribution of these Ca^{2+} sources also are altered during aging and AD (Oddo et al., 2003; Stutzmann et al., 2006).

Given that accumulation of oxidative modifications may contribute to aging itself and to the development of a broad spectrum of neurological disorders (Aluise et al., 2011; Butterfield and Perluigi, 2017; Sultana et al., 2006), the study of ROS in the brain has been more focused on its pathological role (Fig. 2). For instance, when heavy metals such as iron accumulate in the brain, they promote oxidative stress triggering the attack to cellular components such as membranes, proteins, and DNA (Rouault, 2013; Wadhwa et al., 2019). Besides ferritin, a non-heme protein that accumulates iron (Theil et al., 2012) increases in the aged human brain (Zecca et al., 2004). Mitochondrial iron accumulation occurs during the aging process and contributes to the mitochondrial dysfunction observed with age (Seo et al., 2008).

Notably, increased iron concentrations accompany initial aggregation and accumulation of Aβ in specific brain regions, primarily represented by the hippocampus, which is more vulnerable to the development of neurodegenerative alterations leading to AD (Ward et al., 2014). Moreover, iron ions promote not only amyloid β peptide (Aβ) accumulation (Silvestri and Camaschella, 2008; Boopathi and Kolandaivel, 2016; Tahmasebinia and Emadi, 2017; Galante et al., 2018) but also tau aggregation (Ahmadi et al., 2017; Lane et al., 2018) (Fig. 2).

During AD, the generation of ROS and RNS exacerbates in the presence of Aβ. Aβ is generated by the proteolytic cleavage of the amyloid precursor protein (APP) by the following actions of β- and ©-secretases, resulting in the release of the soluble β-cleaved APP fragment (sAPPβ) and the Aβ respectively. Aβ forms soluble oligomers (sAβOs) that can diffuse and bind to several postsynaptic partners, including NMDAR and type 1 metabotropic glutamate receptor 5 (mGluR5). At the presynaptic compartment, the exacerbated phosphorylation of Tau induced by ROS, RNS, elevated Ca^{2+} and sAβOs, promotes the destabilization of microtubules and the consequent impairment in axonal trafficking and neuronal integrity (Fig. 2).

Aging produces structural and neurophysiological changes associated with cognitive impairment (Ianov et al., 2017; Kumar et al., 2018; VanGuilder et al., 2011), although not everyone experiences the same decline level and not all brain regions are affected in the same way. Thus, there is individual variability in cognitive deficits observed with age (Stadtman, 2002). A proportion of older adults exist who achieve healthy management up to remarkably advanced ages (Heyn et al., 2012). Accordingly, the comparison between these types of populations in rats showed up a correlation between oxidative damage in the hippocampus and alterations in learning tasks in aged animals with cognitive impairment, compared to asymptomatic old rats (Nicolle et al., 2001).

A series of studies in hippocampal slices of aged rats showed alterations in LTP (Arias-Cavieres et al., 2017; Boric et al., 2008; Rosenzweig and Barnes, 2003), and increased susceptibility to the induction of long-term depression (LTD), another type of synaptic plasticity (Milner et al., 2004). Also, there is a significant correlation between LTP deficit and altered memory in aged animals (Arias-Cavieres

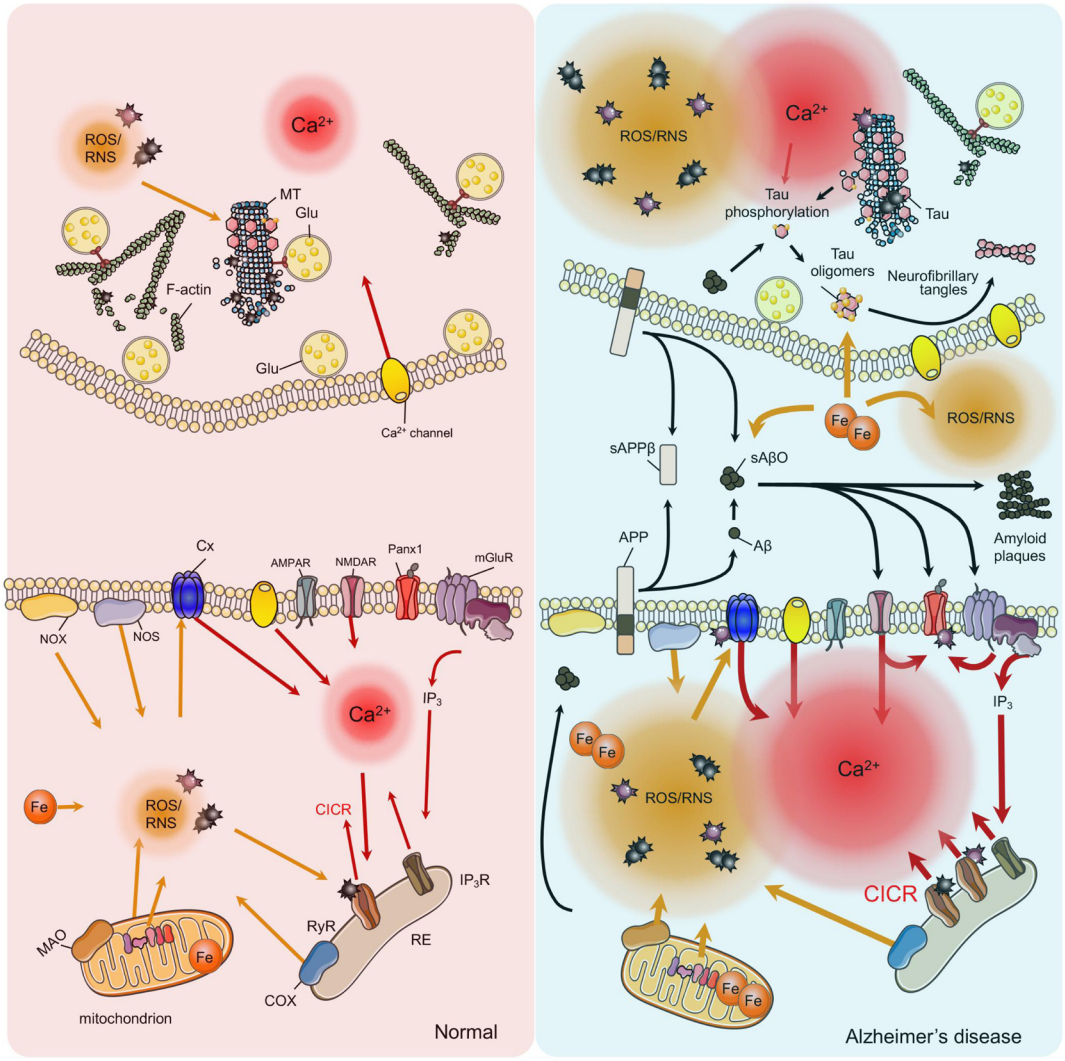

Fig. 2. Redox signaling in normal conditions and Alzheimer's disease. In a physiological context, ROS and RNS can modulate the activity of several channels and receptors, including ryanodine receptors (RyR), connexin, and pannexin channels that contribute to the basal Ca^{2+} and activity-induced Ca^{2+} influx. In turn, the increase in cytosolic Ca^{2+} activates the release of Ca^{2+} from the endoplasmic reticulum (ER) by RyRs and IP3Rs through a Ca^{2+}-induced calcium release (CICR) mechanism that amplifies Ca^{2+} signaling. ROS and RNS can also modulate the activity of RyR, further increasing the cytosolic Ca^{2+} concentration. ROS and RNS modify microtubule- and actin filament (F-actin)-dependent cytoskeleton affecting axonal transport and glutamate (Glu) release. At the postsynaptic site, increased Ca^{2+} levels activate Ca^{2+}-dependent signaling affecting the NMDAR- dependent synaptic plasticity (see text). During AD, the generation of ROS and RNS exacerbates in the presence of amyloid β peptide (Aβ). Aβ originates from the proteolytic cleavage of the amyloid precursor protein (APP). sAβOs can diffuse and bind to several postsynaptic partners including NMDARs and pannexin 1 channels (Panx1) enhancing the Ca2+ influx. sAβos can further aggregate to form insoluble and fibrillar amyloid plaques. sAβOs and amyloid plaques can induce ROS production and oxidative stress. At the presynaptic compartment, the exacerbated phosphorylation of Tau induced by ROS, RNS, elevated calcium and sAβOs, promotes the destabilization of microtubules and the consequent impairment in axonal trafficking and neuronal integrity.

et al., 2017; Boric et al., 2008). Interestingly, in behaviorally characterized aged rats, the LTP mediated by NMDAR is impaired in aged rats with poor cognitive performance. By contrast, LTP mediated by VDCCs is increased only in animals that maintain their cognitive abilities (Boric et al., 2008). Several studies associated the deficits in plasticity and memory in old animals with increases in oxidative stress (Cantuti-Castelvetri et al., 2000; Serrano and Klann, 2004; Bodhinathan et al., 2010a,b; Massaad and Klan, 2011; Kumar et al., 2018), which can result in aberrant activation of various redox-sensitive proteins.

Redox proteomics is, therefore, a promising technique that allows specific evaluation of oxidative modifications of different proteins associated with pathologies related to oxidative stress. Some studies have shown oxidative damage of proteins in the early stages of AD, even before the onset of symptoms. In these studies, proteins with different degrees of oxidation exist, depending on whether the individual is a control, has a mild cognitive impairment (MCI), or is an AD patient (Butterfield and Perluigi, 2017; Butterfield et al., 2012, 2006). It is critical to expanding the search to other markers such as miRNAs, oxidized miRNAs (Wang et al., 2015), or other oxidized proteins, which could be useful markers of cognitive status such as those that we will discuss in the following sections.

5. Ryanodine Receptors (RyR) – redox-sensitive Ca^{2+} channels

RyR act as redox sensors (Fig. 3) (Xia et al., 2000a; Zissimopoulos et al., 2007), modulating different processes such as neuronal development, apoptosis, gene transcription, synaptic transmission and neuronal plasticity (Hidalgo and Arias-Cavieres, 2016). The brain expresses three particular isoforms of RyRs (Furuichi et al., 1994). Hippocampal RyR has a critical role in many forms of synaptic plasticity (Lu and Hawkins, 2002). Studies conducted using isolated RyR channels from rat cerebral cortex have shown that RyR obtained from brain display

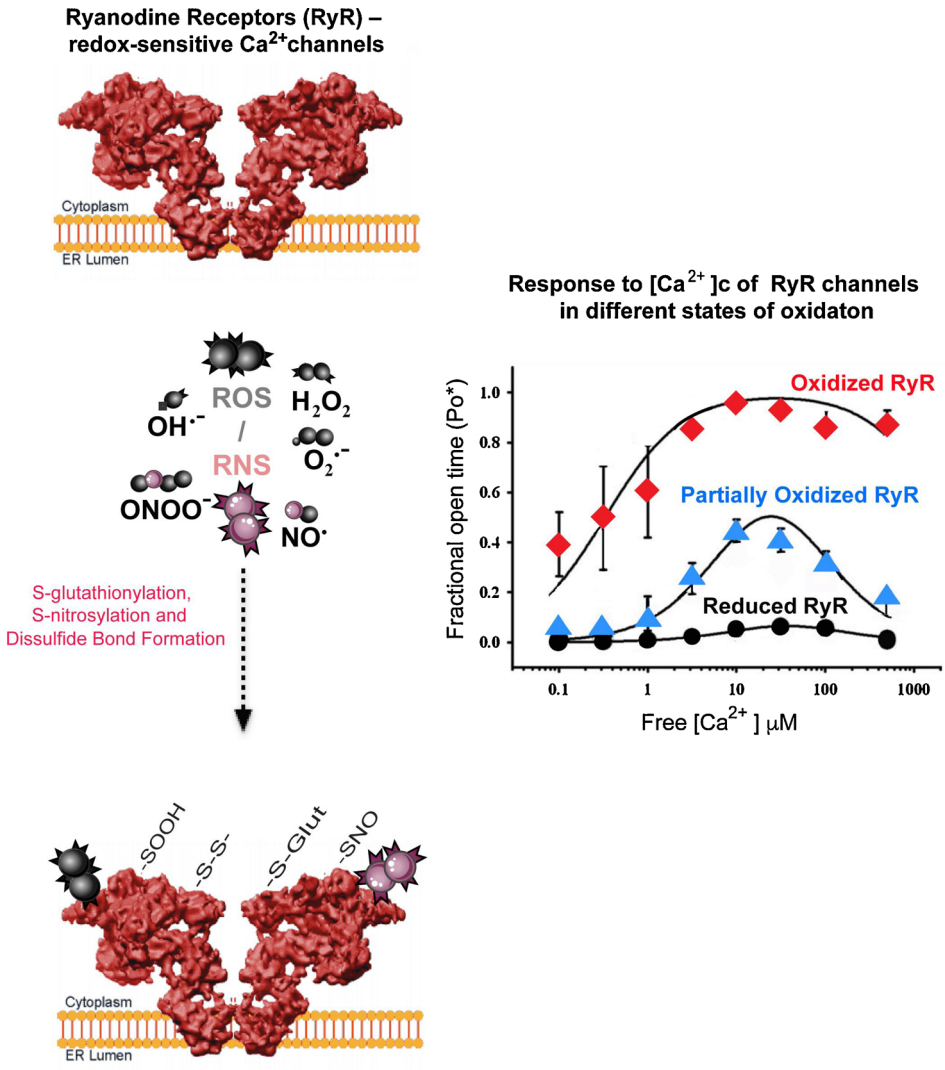

Fig. 3. Redox regulation of Responses to cytoplasmic [Ca^{2+}] of RyR channels: Reactive oxygen and nitrogen species (ROS/RNS) including $O_2^{-\bullet}$, H_2O_2, $OH^{\bullet}$, and $ONOO^{-\bullet}$ causes post-translational modifications of RyR, including S-glutathionylation, S-nitrosylation, and disulfide bond formation (Hidalgo and Donoso, 2008; Paula-Lima et al., 2014). Oxidative modifications of RyR modify the responses to cytoplasmic [Ca^{2+}] of RyR channels from the heart, muscle, and brain. The graph shows the fractional open times (**Po***) of low (circles), moderate (triangles), and high (diamonds) activity channels as a function of free [Ca^{2+}]. Symbols and error bars depict mean and SE values, respectively (Bull et al., 2008). Incubation of RyR channels with reducing agents increases K_a and decreases K_i, while oxidation/alkylation of free sulphydryl residues present in native RyR channels decreases K_a and/or increases K_i (Marengo et al., 1998).

similar biophysical properties than the channels found in the skeletal muscle. In both cell types, the binding of [3 H]-ryanodine to RyR increases in response to Ca^{2+} at micromolar range concentrations, while both Ca^{2+} and Mg^{2+} decreases this binding at millimolar concentrations (Bull et al., 2007, 2003; Marengo et al., 1998). On the other hand, both ATP and caffeine enhance [3 H]-ryanodine binding to RyR (McPherson and Campbell, 1993; Padua et al., 1994; Smith and Nahorski, 1993; Zimanyi and Pessah, 1991).

RyR channels have three types of responses to Ca^{2+}: low, moderate or high activity, depending on the oxidation state (Fig. 3) (Marengo et al., 1998). The explanation of this behavior resides in the multiple reactive cysteines. RyR type 1 (RyR1) is composed of 5037 amino acid residues, of which 100 are cysteines, and only a small number of these are sensitive to redox modulation at physiological pH (Fill and Copello, 2002; Liu et al., 1994). RyR2 has 90 cysteine residues, and 21 of them are reactive (Donoso et al., 2011; Xu et al., 1998), thus different oxidizing agents increase channel activity (Aracena et al., 2003; Marengo et al., 1998; Sun et al., 2001). Conversely, reducing agents such as GSH decrease their activity (Eu et al., 2000; Xia et al., 2000b). Studies carried out with alkylating agents in combination with mass spectroscopy have shown that twelve residues are alkylated in RyR1, suggesting a higher sensitivity of these residues to the redox modifications (Voss et al., 2004). Also, Cys 3635 participates in the formation of disulfide bridges with cysteine residues in the 1-2401 region of RyR1, possibly with Cys 36, 2326, or 2363. In RyR2, Cys 3602 would correspond to Cys 3635 in RyR1 (Mi et al., 2015). In neuronal cells, RyR channels act as coincidence detectors of the Ca^{2+} increase and ROS production induced by activation of N-methyl-D-aspartate (NMDA) receptors (Gleichmann and Mattson, 2011; Munoz et al., 2011; Paula-Lima et al., 2011; Riquelme et al., 2011).

On a physiological level, RyR contributes to regulating axonal outgrowth in cultured hippocampal neurons (Wilson et al., 2016); in a mechanism that involved a feed-forward mechanism linking RyR and NOX2 functions (Wilson et al., 2016, 2015). Interestingly such a molecular mechanism can indeed control actin dynamics as Rac1 exert dual functions as a master regulator of actin polymerization and a fundamental activator of NOX enzymes (Acevedo and Gonzalez-Billault, 2018).

Anomalous RyR channel function occurs in AD pathology (Del Prete et al., 2014; Oules et al., 2012), in which the sAβOs seem to play a central role. Sub-lethal concentrations of AβOs generate low-amplitude but sustained cytoplasmic Ca^{2+} signals that arise from RyR-mediated amplification of Ca^{2+} influx via NMDA receptors in primary hippocampal neurons (Paula-Lima et al., 2011); these anomalous Ca^{2+} signals lead to mitochondrial and NOX2-mediated ROS generation (SanMartin et al., 2017) and glial activation with the increase of expression of proinflammatory cytokines (Munoz et al., 2018). AβOs injections intra-hippocampus of rats significantly decreased the protein content of RyR2 channels. However, RyR channels obtained from AβOs–injected hippocampus displayed with higher frequency the moderate and high activity responses to Ca^{2+}, which is a strong indication that these RyR channels are more oxidized than RyR channels

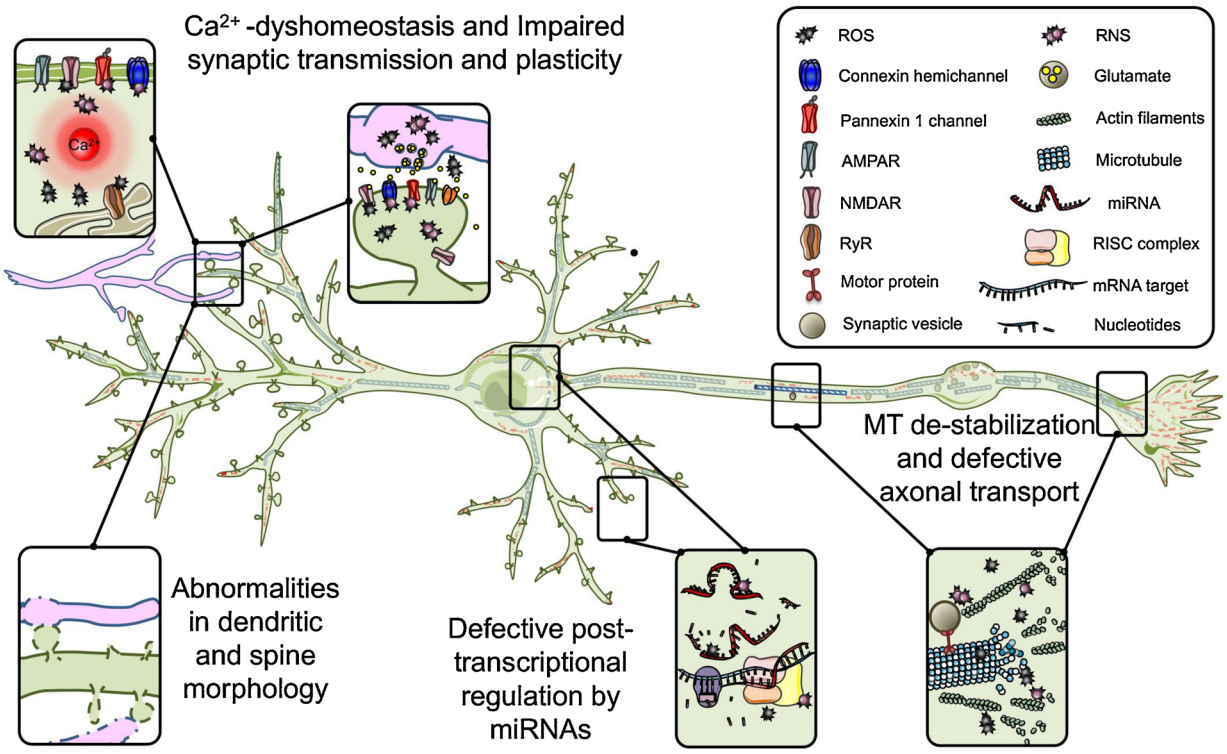

Fig. 4. Overview of the impact of REDOX modifications on neuronal function and structure: ROS and RNS also trigger modifications in the membrane proteins critical for neuronal communication. Increased levels of ROS also impair mitochondrial function and hence bioenergetics balance and neuronal metabolism. Accordingly, redox modifications can alter ionic channels, neurotransmitter receptors (NMDAR and RyR), non-selective channels (Pannexins and Connexins), actin- and microtubule-dependent cytoskeleton, impacting neuronal and synaptic morphology, thus affecting the integrity of dendritic spines and axonal terminals. ROS and RNS can induce alterations in gene expression at the posttranscriptional level by changing the stability, function, and synthesis of miRNAs.

obtained from sham rats (More et al., 2018a). These findings would imply that only RyR channels with oxidized cysteine residues would be responsive to activation by Ca^{2+} – an essential feature of cellular RyR-mediated CICR. Therefore, oxidative stress would favor an aberrant activation of RyR, which causes memory defects associated with aging (Arias-Cavieres et al., 2017; More et al., 2018a, b).

6. Connexin and pannexin proteins

Connexins (Cxs) and pannexins (Panxs) are two protein families involved in cellular communication (Fig. 4) that are also susceptible to redox modification (D'Hondt et al., 2013; Retamal, 2014). At the physiological level, neuronal Cx hemichannels and Panx channels participate in the modulation of synaptic transmission, neuronal plasticity (Ardiles et al., 2014; Prochnow et al., 2012), learning and memory (Frisch et al., 2005; Gajardo et al., 2018) and neurogenesis (Kunze et al., 2009; Liebmann et al., 2013; Wicki-Stordeur and Swayne, 2013; Wicki-Stordeur et al., 2016). Although non-related in terms of homology, Cxs and Panxs exhibit a similar topology, i.e., four transmembrane domains, two extracellular loops, one intracellular loop and both C- and N-terminals in the intracellular space, which enables them to form functional channels or hemichannels at the plasma membrane, allowing the release of signaling molecules (Decrock et al., 2015). However, a critical difference between them is that Cxs hemichannels can form gap junction channels (Saez et al., 2003). Humans and mice express at least 20 isoforms of Cxs and three isoforms of Panxs: neurons express Cx30, Cx36, Panx1, and Panx2, astrocytes express Cx43 and Panx1, microglia express Cx43, Cx32 and Panx1, and oligodendrocytes Cx29, Cx32 and Panx1 (reviewed in (Decrock et al., 2015)).

Diverse evidence supports a link between Cxs/Panxs and redox modulation (Fig. 4). For instance, NO and NO donors induce Cx43 hemichannel opening by S-nitrosylation of cysteine residues (Retamal et al., 2006). In hemichannels formed by Cxs (such as Cx45) lacking cysteines, hemichannel opening does not occur in response to NO and NO donors (Retamal et al., 2007). The increased Cx hemichannel activity in response to NO and NO donors disappeared in the presence of GSH (Retamal et al., 2006). Additionally, Cx46, Cx37, and Cx40 hemichannels activity increases, whereas Cx32 hemichannels conversely close in the presence of NO (Figueroa et al., 2013; Retamal et al., 2009).

Panxs channels activity also participates in redox signaling (Retamal, 2014). Panx1 channels remain closed by reducing agents (Bunse et al., 2010). Substitutions of the cysteine residues Cys40 and Cys346 with alanine on the carboxy-terminal of Panx1 prevent the S-nitrosylation induced by NO donor (GSNO) (Lohman et al., 2012). Moreover, Cys346 replacement with serine leads to a constitutively open Panx1 channel (Bunse et al., 2010). On the other hand, Panx1 channels can permeate NO (Campanucci et al., 2012), and ATP released by Panx1 channels can promote the production of ROS (Onami et al., 2014). These findings support the notion that Cxs/Panxs play a pivotal role in oxidative stress, and that are both modulated by redox modifications.

Additionally, inflammation and conditions where ROS and RNS levels reach high levels (Blaser et al., 2016), associated with aberrant Cxs and Panxs hemichannel activities occur in different brain cells, and neuronal death (Bargiotas et al., 2011; Meme et al., 2006; Orellana et al., 2011a). Panx1-overactivation associates with aberrant activity of NMDAR (Thompson et al., 2008) and/or mGluR5 glutamate-receptors (Lopatář et al., 2015) leading to excitotoxicity and neuronal injury. Aβ induces a cascade of hemichannel activation that promotes the release of glutamate and ATP by glial cells, causing neuronal death (Orellana et al., 2011b). Moreover, there is a correlation between sAβOs levels and increased expression and activity of Panx1 channels in an AD model (Flores-Munoz et al., 2020). Therefore, considering their role in

the modulation of neural activity, Cxs hemichannels, and Panxs channels could be related to harmful conditions associated with aging, such as AD.

7. Microtubule redox modifications

Neuronal functions depend on the intrinsically polarized nature of nerve cells. Microtubules arrays in neurons are not entirely equal between the axon and somatodendritic compartments (Fig. 4) (Kapitein and Hoogenraad, 2015). While axonal microtubules display a polarity with all their plus-ends pointing out to cell periphery, dendritic microtubules have their plus-ends either pointing to cell periphery or cell body (Baas et al., 1988). Thus, axonal microtubules are modulated by Tau protein (Cleveland et al., 1977), while dendritic microtubules contain microtubule-associated protein (MAP)-2 (Kim et al., 1979; Vallee and Borisy, 1978). These two MAPs stabilize neuronal microtubules, contributing to determine the neuronal shape. They also control intracellular trafficking and provide a scaffold for cell signaling.

Tau protein has four tyrosine residues, which can be nitrosylated (Reynolds et al., 2006). Tau can also be modified *in vitro* by peroxynitrite in the absence of tyrosine residues producing lysine-formylated Tau species (Vana et al., 2011). Redox-modified Tau cannot bind efficiently to neuronal microtubules, thereby inhibiting most of its canonical functions as a cytoskeleton stabilizer.

MAP1B is another axonal MAP that contributes to axonal outgrowth in the central nervous system (DiTella et al., 1996; Gonzalez-Billault et al., 2001) and its light chain 1 subunit can be nitrosylated (Stroissnigg et al., 2007). MAP1B association to microtubules is increased upon nitrosylation, leading to the collapse of neurites. While the effects of Cys oxidation in MAPs are still unknown, transitions between oxidized and reduced forms likely play a role in local microtubule stabilization. Moreover, intracellular transport could also be regulated as nitrosylated MAP1B can change the dynein-dependent retrograde movement of cargoes (Stroissnigg et al., 2007). The second layer of regulation is the redox modification of tubulin heterodimers. α- and β-Tubulin contain cysteine residues that are susceptible to oxidation, and they can be naturally modified by metabolites present in food, suggesting that to some extent transient redox changes affecting microtubule proteins may have a role in neuronal physiology (Gruhlke et al., 2019; Wilson and Gonzalez-Billault, 2015). Tubulin can also be temporarily glutathionylated (Landino et al., 2004), which regulates microtubule dynamic properties. Increased glutathyonilated tubulin was concomitant with a decrease in tubulin tyrosination (Carletti et al., 2011), which is associated with the presence of highly dynamic microtubules that are essential to maintain neurite elongation. Reduced tyrosination severely affects axonal elongation and guidance (Erck et al., 2005; Utreras et al., 2008). Maintenance of a high population of tyrosinated microtubules could be a mechanism to increase the labile fraction of microtubules, which may be necessary to rapidly enhance axon outgrowth (Qiang et al., 2018). Besides, microtubules tyrosination is also essential as a molecular signature that provides specificity to intracellular trafficking.

Additionally, redox proteomics approaches determined that during rodent and human aging, tubulin is abnormally oxidized (Wang et al., 2017). The presence of redox-modified Tau was observed *in vitro* (Reynolds et al., 2005) and *in vivo* (Reyes et al., 2012). Nitration at tyrosine 29 seems to be, therefore, a useful marker of pathological tau redox modifications since it increases in corticobasal degeneration, progressive supranuclear palsy, and AD (Reyes et al., 2012). Therefore, changes in post-translational modifications of microtubules seem to correlate to redox modifications, affecting microtubule proteins functionally.

8. Redox regulation at the post-transcriptional level

Given the importance of the redox signaling pathways, it becomes essential to develop mechanisms to modulate them quickly. Among the regulatory mechanisms involved in the control of oxidative stress, post-transcriptional gene regulation mediated by miRNAs emerges as crucial in modulating redox signaling and also aging (Banerjee et al., 2017; Emde and Hornstein, 2014). The miRNAs are endogenous small non-protein-coding RNAs that act as essential gene repressors through their ability to degrade their target messenger RNAs and/or induce translational repression (Fig. 4) (Bartel, 2009; Lagos-Quintana et al., 2001). One of the main pieces of evidence for miRNAs having a pivotal role in the regulation of cellular redox homeostasis comes from the fact that Dicer, a key enzyme of the miRNA biogenesis machinery responsible for synthesis of mature functional miRNAs (Kim, 2005), is down-regulated by aging and by oxidative stress, which results in altered miRNA expression and pathological phenotypes (Ungvari et al., 2013). Also, miRNAs themselves may be modified by the redox status, which may, in turn, alter miRNA stability and functionality (Paulsen et al., 2011). For example, miR-9, miR-21, miR-200, and miR-210 may be regulated by ROS while they may also regulate ROS levels (Jajoo et al., 2013; Lin et al., 2009). Furthermore, ROS-sensitive transcription factors such as NFκB, p53, Nrf2, or HIF1α can mediate ROS regulation of miRNA expression (Greco et al., 2018; Singh et al., 2013). Of importance, the existence of redox-sensitive miRNAs, named "redoximiRs" (Cheng et al., 2013), which regulate not only key enzymes involved in the generation of ROS, but also the transcription factors that control cellular responses to oxidative stress, is only one example of the importance of miRNAs on the regulation of redox-signaling pathways. One of the best-known redoximiRs is miR-155, which plays an essential role in controlling ROS and NO production (Liu et al., 2015). Silencing of miR-155 decreased apoptosis and ROS production while promoting NO generation, suggesting a protective effect for the miR-155 deficiency (Liu et al., 2015). The miRNAs miR-23b and miR-25 also regulate Nox 4 (Fu et al., 2010; Im et al., 2012). Another study showed miR-743a as a redoximiR that, through regulation of the malate dehydrogenase enzyme in a mouse hippocampal cell line, can regulate the neuronal mitochondrial redox state (Shi and Gibson, 2011). These findings indicate that miRNAs are essential in controling oxidative stress and preventing ROS-mediated damage to neurons.

9. miRNAs as biomarkers of aging

Oxidative stress not only affects proteins but also affects the expression of different miRNAs that could function as molecular biomarkers of aging. AD patients and aging mouse models present an upregulation of miR-34 (Emde and Hornstein, 2014). Due to the involvement of miR-34 in the regulation of aging-related processes, it is considered a “geromiR”, a growing group of miRNAs implicated in aging (Ugalde et al., 2011). The aging-related action of miR-34 is achieved at least partially through the direct regulation of sirtuin 1 (Sirt1) (Li et al., 2011), an NAD+-dependent deacetylase involved mainly in maintaining antioxidant defense during aging (Houtkooper et al., 2012). Also, miRNAs are known to participate in the regulation of redox signaling pathways that contribute to pathological processes such as mitochondrial dysfunction (Subramaniam and Chesselet, 2013).

Fig. 4 shows an overview of the impact of redox modifications on neuronal function and structure, highlighting that ROS and RNS can induce alterations in gene expression at the posttranscriptional level by affecting the stability, function, and synthesis of miRNAs. Also, Fig. 4 shows that ROS and RNS trigger redox modifications that alter the function of several proteins, including ionic channels, neurotransmitter receptors (NMDAR and RyR), non-selective channels (Pannexins and Connexins), actin-, and microtubule-dependent cytoskeleton. These redox modifications might impact neuronal and synaptic morphology and affect the integrity of dendritic spines and axonal terminals. Therefore, it is reasonable to propose that oxidative modification in both proteins and miRNAs as possible targets to fight the symptoms of brain aging, as well as suitable putative biomarkers of aging itself. Also,

these modifications could be useful in evaluating the effectiveness of some therapies, such as diet antioxidant consumption in neuronal aging, such as the ones that will discuss next.

10. Diet antioxidant consumption and neuroprotection

There are several studies conducted to investigate the therapeutic effects of antioxidant therapy to treat several clinical neurological conditions and aging. In this context, a study performed in Okinawa, Japan, analyzed the factors contributing to centenarians successful aging. This study found that the increase in lipid peroxidation associated with age was absent in this population, which correlated with a diet rich in antioxidants (Suzuki et al., 2010). The effects of antioxidants are positive in diverse in vitro and in vivo models of aging and disease, and some populations have shown increased longevity associated with antioxidant diets. Nevertheless, clinical trials all over the world have been controversial and even confusing regarding the real benefit that an antioxidant-based diet could have. The possible explanations for these discrepancies are varied. The immense diversity of diet-derived antioxidants, their bioavailability, and intestinal absorption that depend mainly on the individual microbiota could determine the effect of the polyphenols on the population (Filosa et al., 2018). Therefore, in this section, we will only review some antioxidants whose effects have been proven in humans to counteract oxidative stress and to enhance cognition.

11. Polyphenol health effects on neurodegenerative disorders

While many observational and intervention studies have suggested a positive relationship between the consumption of polyphenol-rich products and the improvement in cognitive performance (Cicero et al., 2018; Haller et al., 2018; Pervin et al., 2019), the lack of convincing results in clinical trials makes it difficult to conclude the exact effects of these molecules on cognitive status and neurodegeneration. For example, a meta-analysis of the impact of the Mediterranean diet on mild cognitive impairment (MCI) did not report a significant benefit (Radd-Vagenas et al., 2018). Another meta-analysis considering 21 clinical trials was also unable to demonstrate a beneficial action of Ginkgo biloba (Gb), whose extract is rich in polyphenols in patients with MCI (Yang et al., 2016). However, a more recent meta-analysis concluded that Gb extract does exert potentially beneficial effects on specific neuropsychiatric parameters, when administered for at least five months, at doses higher than 200 mg/day (Yuan et al., 2017). These findings are consistent with previous data obtained from patients with mild to moderate dementia (vascular dementia or AD), which exhibited improved behavioral performance after Gb treatment (Ihl, 2013).

11.1. Curcumin

Curcumin is one of the few molecules with a positive demonstrated effect on brain aging. The molecular structure of curcumin gives it the ability to cross the blood-brain barrier (BBB), making it a crucial molecule for a possible treatment to attenuate or delay the effects of aging in the brain. A study conducted in Singapore found that older people (60–93 years) who occasionally or frequently consumed curry (curcumin-containing spice), achieved significantly better cognitive performance than people who never consumed this spice (Ng et al., 2006). However, a randomized, double-blind study, with 36 subjects diagnosed with mild to moderate AD selected to participate in a 24-week receiving placebo 2 or 4 g of curcumin complex (curcumin and other curcuminoids), was not able to demonstrate a clinical effect against AD (Ringman et al., 2012). Subsequent studies showed that the bioavailability of curcumin could play an essential role in the impact it has on age. A randomized, double-blinded, placebo-controlled study of 60 non-demented adults between 60 and 85 years who consumed acutely and chronically a lipid formulation of curcumin, also showed a better working memory in number subtraction tasks than controls. Also, the chronic treatment achieved an improvement in non-cognitive domains such as mood and general satisfaction, as well as decreased general physical fatigue measured by the Chalder Scale (Cox et al., 2015). As previously reported, elderly subjects improved their behavioral symptoms associated with AD after 12 weeks of turmeric treatment, measured with Neuropsychiatric Inventory (NPI), which allows assessment of the non-cognitive clinic in patients with dementia, and provides monitoring of the effectiveness of treatments on these symptoms (Hishikawa et al., 2012). Finally, a randomized, double-blinded, and placebo-controlled study with 160 asymptomatic elderly subjects in Australia, used an optimized oral bioavailability curcumin formulation for 48-weeks. Comprehensive cognitive assessments performed at baseline, 24 weeks, and 48 weeks of treatment based on the Montreal Cognitive Assessment (MoCA) score revealed that in the 24th week, the group that consumed curcumin presented a score significantly higher in the MoCA compared to the placebo group. However, at 48 weeks, the cognitive difference was not present (Rainey-Smith et al., 2016).

11.2. N-acetylcysteine (NAC)

NAC is a derivative of the amino acid cysteine that has an acetyl group ($-COCH3$) attached to its nitrogen atom. Besides, it has a thiol group, which can be oxidized with a wide variety of radicals and can act as a nucleophile (Samuni et al., 2013). The GSH structure, which has a negative charge at pH 7.4, goes into its neutral form at pH < 3.3, which allows its penetration through the membrane from the gastric fluid (pH 1.5–3.3) by passive diffusion. Once NAC enters the systemic circulation via gastric or by other intravenous routes, it can only leave the blood vessels after N-deacetylation by hydrolysis. Alternatively, NAC may suffer from deacetylation and then enter the cell by transporting through the alanine-serine sodium transporter- cysteine (ASC) or by a less efficient hetero-exchange with glutamate-cystine in astroglial cells (Samuni et al., 2013). After the entry of NAC into the cell, hydrolysis quickly releases cysteine, which is a precursor of the endogenous antioxidant GSH. As previously mentioned, GSH is crucial to cellular antioxidant activity, to cell signaling regulated by redox (oxidation reaction) and also to immune responses. GSH is synthesized intracellularly by the subsequential actions of γ-glutamylcysteine synthetase and GSH synthetase (Arakawa and Ito, 2007; Samuni et al., 2013). NAC presents the ability to increase the availability of intracellular cysteine and GSH. Furthermore, NAC presents a neuroprotective effect, constituting a promissory neuroprotective agent to counteract oxidative stress in aging and ND. Several works performed *in vivo* in animal models showed that the supply of NAC restored memory deficit and decreased oxidative stress associated with aging and AD, generating a decrease in the levels of oxidation, lipid peroxidation and carbonylation of proteins in these models (Huang et al., 2010; Martinez et al., 2000; More et al., 2018a). The potential of NAC in promoting cognitive health and alleviating cognitive decline associated with dementia has been recently revised (Hara et al., 2017). Although no studies have looked at the prevention of cognitive decline or dementia in humans with NAC, nutraceutical formulations containing NAC, among other components such as vitamin B12, were associated with cognitive enhancement and preservation of executive function in MCI patients (Remington et al., 2015). In a double-blind, randomized controlled trial of 106 AD patients, the same nutraceutical formulation as above, resulted in significant improvements in the dementia rating scale and executive function compared to the placebo group (Remington et al., 2016). However, treatment with NAC alone showed less robust effects in probable AD patients, with improvement in letter fluency task but not in the Mini-Mental State Examination score. Interestingly, multiple meta-analyses have reported that NAC is generally safe and well-tolerated for most adults (Cazzola et al., 2015; Remington et al., 2015, 2016). We postulate that, as in the case of other previously affected antioxidants, it is most likely that an increase in dose and treatment

time would increase the benefits of supplementation with this antioxidant

11.3. Resveratrol

Resveratrol (RV) and its derivative pterostilbene are other antioxidants that can cross the BBB and influence brain activity, as has been shown in several studies (Ramirez-Garza et al., 2018). In healthy elderly adults, RV supplementation (200 mg daily for 26 weeks) improved episodic memory (Witte et al., 2014). Also, RV significantly increases resting functional connectivity between the hippocampus and angular cortex, compared with controls that did not receive RV (Kobe et al., 2017). The RV-receiving group exhibited a lower concentration of glycosylated hemoglobin, suggesting that RV may act on neuronal function, causing improvements in energy metabolism similar to caloric restriction (Baur and Sinclair, 2006).

A recent study described the effects of the consumption of RV-containing formulation (derived from grapes) in 72-year-old individuals with MCI (Lee et al., 2017). One group was supplemented twice a day for six months with the RV-rich formulation, and the other group received only the placebo. A battery of neuropsychological tests was applied to assess cognitive performance, together with emission tomography of positrons combined with fluorodeoxyglucose to assess brain metabolism. In the neuropsychological tests performed, no significant differences existed between the two groups; however, the placebo group experienced a significant deterioration in the cerebral metabolism of the right posterior cingulate cortex, and the left superior temporal posterolateral cortical cortex, a deterioration that did not manifest in the group that received the supplementation. Also, the cerebral metabolism in the upper right and left parietal cortex, and the inferior anterior temporal cortex correlated with improvements in other cognitive domains such as attention and working memory (Lee et al., 2017).

In a more neurodegenerative context, there are few clinical trials of RV on pathologies associated with aging. On the other hand, the data that emerges is controversial, suggesting that classic biomarkers that account for the pathologies are probably not the ones that best predict a possible RV effect. For example, in a randomized, double-blinded, placebo-controlled trial, performed in individuals with mild to moderate AD, RV was evaluated after chronic administration at a dose of 500 mg/day with 500 mg increments every 13 weeks up to 52 weeks, ending at 1000 mg twice daily for each patient. Remarkably, both the group supplemented with the RV and the placebo showed a decrease in the levels of the Aβ -40 peptide in the cerebrospinal fluid (CSF) at 52 weeks (Turner et al., 2015). Another subsequent study found similar results when evaluating the Aβ -42 amyloid peptide in the CSF (Moussa et al., 2017). However, this study showed that RV produces a significant plasma increase in the expression of MMP10 matrix metalloproteinase, as well as a reduction in two of the interleukin IL-12 subunits, suggesting that RV can also regulate neuroinflammation in patients with AD.

The need for more studies on the efficacy of RV in AD is evident since inflammation biomarkers could be better predictors of the disease status than the classic Aβ peptide. In this sense, one study attributes a critical role to neuroinflammation in the pathogenesis of dementia, as evidenced by the activated microglia found in patients with dementia (Takeda et al., 2014). As a consequence of neuroinflammation, a vicious circle produces more ROS generating additional oxidative stress, probably due to a redox imbalance in organic hydroperoxides derived from serum/plasma lipid peroxidation of patients with AD (Hatanaka et al., 2015).

A large number of 45 to 69-year-old subjects were recruited in urban centers in Central and Eastern Europe to study their memory, verbal fluency, and processing speed, at the start of the study (2002–2005) and three years later. Analysis of biomarkers with cognitive test scores transversely (n = 4304) and prospectively (n = 2882) showed an inverse association between cognitive status and organic hydroperoxide levels, but not in other oxidative parameters measured as total thiols and antioxidant potential (Horvat et al., 2016).

12. Conclusion

Although all the evidence mentioned above supports the use of specific antioxidants to counteract the harmful effects of aging and ND, there is still much controversy surrounding the use of antioxidant treatments for these purposes. The evidence revised here indicates that oxidative driven modifications of specific proteins and changes in miRNA expression may be useful biomarkers for aging and ND. Also, we discussed the literature covering the neuroprotective effects of some particular antioxidants, i.e., polyphenols, curcumin, N-acetylcysteine, and Resveratrol, which have shown protective effects against cognitive deterioration in human aging and AD. We conclude that antioxidant therapies are still underexplored, including potential alternatives with undoubtedly beneficial effects when administered in the correct doses, in the ideal formulation combination, and during the appropriate therapeutic window.

Acknowledgement

DIUV - CIDI N ° 5/06 to PM; Fondecyt 11150776 to AA; Fondecyt 1170446, MAG1895 and MAG1995 to YE-P; ANID/FONDAP 15150012 to CG-B; Chilean State Universities Network grant 1656-1756 (all authors).

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