Review

Mechanisms of neuroplasticity and brain degeneration: strategies for protection during the aging process

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Abstract

Aging is a dynamic and progressive process that begins at conception and continues until death. This process leads to a decrease in homeostasis and morphological, biochemical and psychological changes, increasing the individual's vulnerability to various diseases. The growth in the number of aging populations has increased the prevalence of chronic degenerative diseases, impairment of the central nervous system and dementias, such as Alzheimer's disease, whose main risk factor is age, leading to an increase of the number of individuals who need daily support for life activities. Some theories about aging suggest it is caused by an increase of cellular senescence and reactive oxygen species, which leads to inflammation, oxidation, cell membrane damage and consequently neuronal death. Also, mitochondrial mutations, which are generated throughout the aging process, can lead to changes in energy production, deficiencies in electron transport and apoptosis induction that can result in decreased function. Additionally, increasing cellular senescence and the release of proinflammatory cytokines can cause irreversible damage to neuronal cells. Recent reports point to the importance of changing lifestyle by increasing physical exercise, improving nutrition and environmental enrichment to activate neuroprotective defense mechanisms. Therefore, this review aims to address the latest information about the different mechanisms related to neuroplasticity and neuronal death and to provide strategies that can improve neuroprotection and decrease the neurodegeneration caused by aging and environmental stressors.

Key Words: cell senescence; cell signaling; cholinergic; enriched environment; long-term potentiation; neurodegeneration; neurogenesis; neuroinflammatory; neuronal death; neuroprotection; neurotophin

Introduction

One of the most crucial questions within neuroscience is about understanding the cellular and molecular events involved in neuronal death following acute lesions, such as hypoxia, ischemia, epileptogenic crises, and hypoglycemia, and in chronic events, such as major neurocognitive disorders. Neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis (Rybakowski et al., 2018) and Parkinson's disease are pathologies characterized by the irreversible destruction of certain neurons and progressive and incapacitating loss of certain functions of the nervous system (Fan et al., 2017) and are the main causes of dementia. Neurodegenerative diseases are caused by genetic (mutation of disease-associated genes) and environmental (including the effects of aging and lifestyle) interactions (Herrero and Morelli, 2017). These disorders share common features such as synaptic dysfunction, excitotoxicity, misfolded protein aggregation, production of reactive oxidative species (ROS), mitochondrial dysfunction, intracellular calcium dysregulation and cell loss (Fan et al., 2017). Disrupted cell functions, along with accumulated DNA damage and aging-induced oxidative stress, gradually outperform defense systems, including the protein quality control system (e.g., ubiquitination and autophagy) and others, resulting in increasing cell death (apoptosis) (Hollville et al., 2019). Multiple pathways are likely to be involved in cell death as part of the natural aging process or due to the presence of neurodegenerative diseases. Cell death may occur by stimuli from the cell itself or from toxic factors that activate cell death pathways which include excitotoxicity, oxidative stress and release of senescence-associated secreted phenotypes (SASPs).

Although all these events may occur as part of the aging process, it is now clear that lifestyle may trigger defense mechanisms that can alter the course of aging. These include physical leisure activity (Andel et al., 2016), adequate food intake based on low calorie diets (Wahl et al., 2016), environmental stimulation (Balthazar et al., 2018) and the level of cognitive reserve acquired through formal education (Soldan et al., 2017; Balduino et al., 2020). Most of these strategies were proven to be effective in constructing a brain reserve to delay or prevent the development of several types of dementia in older adults.

In this review, we describe the mechanisms related to neuroplasticity and neurodegeneration and the role of cell

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senescence in the degenerative processes and cell death. We also discuss the effectiveness of several strategies that may create brain protection and increase quality of life in old age.

Search Strategy and Selection Criteria

Search for bibliographic references was performed in US National Library of Medicine of the National Institutes of Health (PubMed.gov). References between 2015 and 2019 were preferentially used, unless classical information was needed. The key-words used as search criteria were: neuroplasticity, neurodegeneration, neuroprotection and brain aging.

Neuroplasticity and Cell Survival

Neuroplasticity is the ability of the brain to change continuously throughout an individual's life, and can be observed at multiple levels, with adaptive behaviors and learning and memory being at the top of the hierarchy, linking structural changes with functionality. The base of this pyramid is formed by molecules and their interactions, consisting of synapses, neuronal circuits and different levels of binding (**Figure 1**). Synapses are specialized sites between neuronal cells that represent the main structure involved in chemical neurotransmission in the nervous system. An elementary principle of neuroplasticity is the morphological changes of synaptic connections that are constantly renewed or recreated, with the equilibrium of these processes being strongly dependent on neuronal activity (Jasey and Ward, 2019). Activity-dependent change in synapses is one of the main points of the concept of neuroplasticity and the learning and memory theories based on experience-induced creation of engrams, physical marks of changes in synaptic structure (Jasey and Ward, 2019).

Important events for cognitive preservation such as memory consolidation can be attributed to cellular and molecular processes that enable the neuron to change its response to a given stimulus. This phenomenon is directly related to greater synaptic efficacy through an electrophysiological alteration called long-term potentiation (LTP), capable of consolidating morphological and functional alterations in synapses over a long period, accompanied by changes in gene transcription and protein synthesis (Petsophonsakul et al., 2017). The molecular events involved in neuroplasticity can be divided into structural (neurogenesis and dendritic spine formation) and functional (changes in the release of chemical mediators, receptor sensitivity and activation of postsynaptic mechanisms) (Kulik et al., 2019).

A major mechanism in the structural neuroplasticity process is hippocampal neurogenesis. This phenomenon is composed of four distinct phases: proliferation, migration, differentiation, and maturation (Kempermann et al., 2018). The cellular precursor found in the hippocampus, especially in the subgranular zone of the dentate gyrus (Volianskis et al., 2015), is a type of astrocyte that expresses important markers of cell proliferation such as glial fibrillary acid protein, proliferating cell nuclear antigen and nestin (Kempermann et al., 2018). After the process of cell division, most cells undergo apoptosis or are phagocytized by microglia (Li and Barres, 2018). Surviving neuroblasts stop expressing cell proliferation-related proteins and start expressing structural proteins such as doublecortin; from that moment on, the association of doublecortin expression, neuronal nuclear protein, calretinin and calbindin characterizes the process of cellular differentiation (Kempermann et al., 2015). These newly generated neurons mature in the granular region of the dentate gyrus and are excitatory glutamatergic neurons. The neurogenesis of these cells is regulated by neurotrophin levels such as brain-derived neurotrophic factor (BDNF). Therefore, stimuli that interfere with BDNF production and activity also influence adult hippocampal neurogenesis (Zhang et al., 2018).

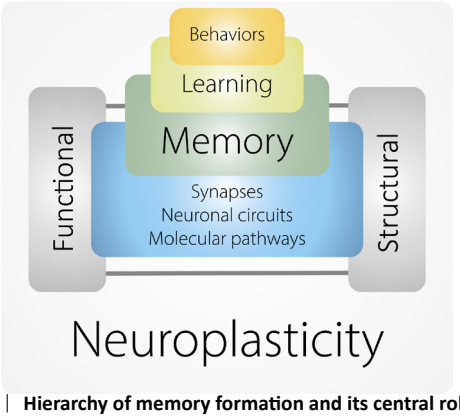

Figure 1 | **Hierarchy of memory formation and its central role linking structural changes with functionality.**
The base of this pyramid is formed by molecules and their interactions, consisting of synapses, neuronal circuits and different levels of binding.

These dynamic changes in the synaptic structural complex are strongly regulated by the interaction between the presynaptic terminal, the postsynaptic region and astrocytes, known as tripartite synapse. Perisynaptic astrocyte processes play an important role in the stabilization and maturation of dendritic spines, influencing the dynamics of neuroplasticity (Haroon et al., 2017; Li and Barres, 2018). Astrocytes express metabotropic and ionotropic receptors, which can be activated by neurotransmitters (norepinephrine, acetylcholine, and glutamate) release. In this way, astrocytes can change, allowing them to detect and modulate the strength of synaptic activity (Verkhratsky and Nedergaard, 2018). The increase in Ca^{2+} levels inside astrocytes depends on the neuronal activity and gives rise to the release of several gliotransmitters (ATP and glutamate) in the synapse, offering multiple ways to control synaptic activity (Rusakov, 2015; Bazargani and Attwell, 2016). In addition, astrocytes are rich in transporters for glutamate, glycine and γ-aminobutyric acid, that are used to remove them from the synaptic cleft and, through enzymes, to convert them into precursors and then, in pre-synaptic terminals, reconverting to active transmitters. Thus, astrocytes clearly contribute to neuroprotection, as they keep levels of extra-synaptic glutamate low to prevent excitotoxicity. In this respect, the literature shows that astrocytes can secrete many cytokines and chemokines, such as interleukin 1 (IL-1), IL-6, chemokine CXC motif ligand-1, IL-8, nuclear factor-kappa B, interferon-γ-induced protein 10, tumor necrosis factor-α, CC motif ligand chemokine, macrophage inflammatory protein 1 alpha, macrophage migration inhibitory factor, and granulocyte- macrophage colony stimulating factor, causing infiltration of circulating leukocytes into the brain and leading to a chronic inflammatory process, which may be caused by perivascular activity of the microglia (Lian and Zheng, 2016; Liebner et al., 2018). Constant activation of glial cells leading to inflammation may be a neurotoxic response that can be closely associated with the progression of neurodegenerative diseases (Osborn et al., 2016; Kawano et al., 2017). Thus, as a response to various forms of insults including ischemia, trauma, and neurodegenerative diseases such as Alzheimer's disease, astrocytes undertake extensive cellular and molecular changes leading to functional alterations in order to actively modulate synaptic plasticity.

Among the functional molecular changes, two systems stand out: the glutamatergic and cholinergic. In the glutamatergic system, N-methyl-D-aspartate (NMDA) receptors are essential mediators of activity- dependent synaptic plasticity that are involved in cognitive functions such as learning and memory (Volianskis et al., 2015). The NMDA receptor has a di- or tri-heteromeric structure and must be composed

of two GluN1 subunits associated with GluN2 subunits or a mixture of GluN2 and GluN3. In the hippocampus, there is a predominance of the diheteromeric structure with GluN1-N2A and GluN1-N2B subunits. As each GluN2 subunit confers unique signaling property transfer capabilities, there has been intense speculation that the composition of the NMDAR subunit results in either LTP or long-term depression (LTD). In Alzheimer's disease, high densities of β-amyloid plaques in the hippocampus are known to induce increased replacement of NMDA Glu-N2A subunits with Glu-N2B (via calpains) facilitating receptor binding to SAP-102, which presents high mobility for extra-synaptic regions (Parsons and Raymond, 2014; Zhang et al., 2016). Thus, instead of NMDA-R2B being internalized by endocytosis for recycling, it will diffuse more intensely laterally to the extra-synaptic site, which is an important center of signaling pathways, leading to apoptotic neuronal death (via caspase-3) (Parsons and Raymond, 2014; Zhang et al., 2016; Bading, 2017). In addition, the literature shows that the anchoring protein PSD-95 binds to cytoskeleton proteins implicated in synaptic connectivity, as well as controlling synapse architecture and morphology (de Wilde et al., 2016); therefore, it is critical for synaptic stabilization and receptor traffic regulation, from recruitment of receptors from the extra-synaptic site to the active zone, to modification of intracellular signaling proteins.

The importance of the cholinergic system for LTP modulation and induction is reported in previous studies showing that in presynaptic neurons the α7 cholinergic receptor induces the synthesis and release of the neurotransmitters involved in the formation of LTP, such as glutamate, as discussed above (Lozada et al., 2012; Haam and Yakel, 2017) (**Figure 2**). In postsynaptic neurons, the same receptor acts on the Ca^{2+}/calmodulin-dependent protein kinase pathway, where membrane- derived Ca^{2+} permeability leads to protein kinase A activation and consequent CREB phosphorylation, which is responsible for regulating the protein synthesis needed to stabilize the synaptic changes that are triggered during learning (**Figure 2**). Its activity is regulated by phosphorylation, mainly in Ser133, through several proteins, among them CAMKIV, which acts as a calmodulin effector and induces an increase in the release of different proteins, such as mature BDNF, which after interaction with its specific receptor tropomyosin receptor kinase B in the postsynaptic membrane, performs its main functions in relation to the growth and differentiation of new neurons and maturation and refinement of dendritic branching (Beeri and Sonnen, 2016; Haam and Yakel, 2017). These stimulations connect cytoskeletal proteins such as the integrin-actin complexes to postsynaptic dendrites, and changes in this system modify the density of dendritic spicules (Lei et al., 2016; Kulik et al., 2019). Thus, contact between axons and dendrites is increased and leads to morphological and/or neurotransmission changes in the synapses.

The alpha7 cholinergic nicotinic receptor plays important roles in neuroplasticity, neuroprotection and memory recovery in both healthy and disease conditions. Recently, our research group showed that the pharmacological antagonism of the receptor prevented memory recovery in mice submitted to an experimental model of neurodegeneration followed by attention training, as a strategy to recover memory (Telles-Longui et al., 2019). Activation of the α7 receptor leads to an increase in phosphorylation of the protein kinase Akt, as the receptor is capable of activating phosphoinsitide 3-kinase (PI3K) through the Janus kinase 2, resulting in the inactivation of glycogen synthase kinase 3 and an increase in Bcl-2, leading to neuroprotection. Activation of the PI3K/Akt pathway may also occur through the binding of BDNF and NGF neurotrophins to their respective receptors. Akt phosphorylation and activation enable cell survival, inhibition of pro-apoptotic Bad protein, and activation of κκB kinase α

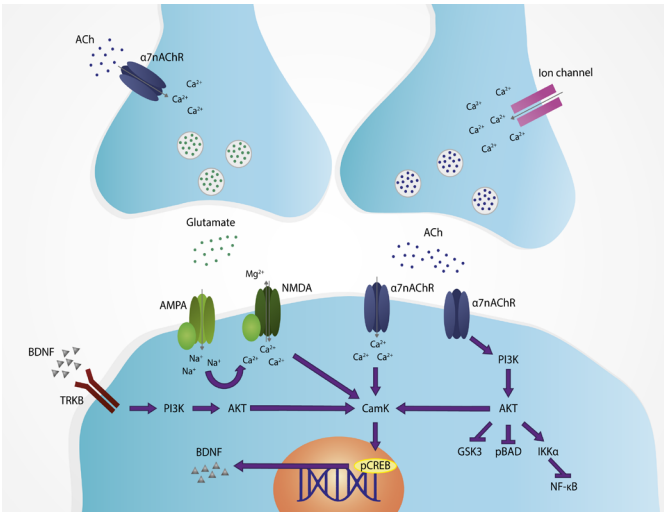

Figure 2 | **Modulation and induction of long-term potentiation by the cholinergic system through the activation of pre-synaptic α7 cholinergic receptor.**
The figure shows the participating pathways in postsynaptic neurons culminating in CREB phosphorylation and consequent stabilization of synaptic changes, triggered during the learning process.

inhibitor, inhibiting NF-κB formation (Lee, 2015).

The participation of BDNF in neuroplasticity is particularly important in both structural changes and synaptic function (Sasi et al., 2017; Kowianski et al., 2018), where BDNF positively regulates the synthesis of proteins involved with synaptic changes (Leal et al., 2015). Further evidence of the importance of BDNF is seen in the presence of this neurotrophin in presynaptic glutamatergic neurons (Sasi et al., 2017). BDNF influences the process of neurogenesis in the dentate gyrus that preferably forms glutamatergic neurons (Leal et al., 2015; Haam and Yakel, 2017), further highlighting its role in both structural and functional neuroplasticity.

In addition to the important role that BDNF plays in neuroplasticity, other neurotrophins also contribute by modulating this process. An example is insulin-like growth factor 1 (IGF-1), which is capable of modulating glutamatergic receptors (Dyer et al., 2016). This growth factor interferes with AMPA receptor viability, promoting clathrin-mediated endocytosis, and making IGF-1 an important LTD modulator. In addition, IGF-1 appears to increase the efficiency of glutamatergic synapses by regulating voltage-dependent Ca^{2+} channels (Dyer et al., 2016; Herrera et al., 2019). IGF-1 is also involved in PI3K/Akt pathway activation, triggering an intracellular cascade capable of promoting cell survival and neuroprotection (Bianchi et al., 2017; Wrigley et al., 2017). Finally, IGF-1 increases TRKB receptor expression, making it more readily available for binding to BDNF (Li et al., 2013).

Mechanisms of Neurodegeneration

Necrosis

Cell death by necrosis is characterized by a pathological process, because when activated, it stimulates the action of the immune system. This type of death can be triggered under extreme conditions such as hypoxia, ischemia, intoxication, drug abuse and autoimmune reactions of neighboring cells (Vanden Berghe et al., 2014; Zhang et al., 2017). The plasma membrane is damaged, which causes loss of cellular protection, increased cytoplasmic and mitochondrial volume, and extravasation of the intra to extracellular content (Lalaoui et al., 2015). This change in the constitution of the cell generates an inflammatory response, with activation of immune system factors such as lymphocytes, macrophages, ILS and transcription factors (TNF)

(Zhang et al., 2017). In addition, the activation of this system also affects neighboring cells and the environment, which can trigger chain death.

During the necrosis process, mitochondrial function changes, decreasing the production of ATP and, consequently, inhibiting the Na^+/K^+-ATPase pump, causing cell swelling due to the increase of sodium ions in the cell cytoplasm (Lalaoui et al., 2015). There is also an increase in calcium in the cytosol that triggers the activation of phospholipases and proteases, resulting in an increase in ROS, which induces rupture of the plasma membrane and the activation of more proteases, provoking the extravasation of the content of the cell (de Almagro and Vucic, 2015). Necrosis was always considered an unintentional cell death resulting from a physicochemical insult. However recent genetic evidence and the advent of pharmacological inhibition of the process has revealed the existence of several pathways of necrosis regulation. This resulted in different forms of cell death (de Almagro and Vucic, 2015; Fan et al., 2017). One of these forms, necroptosis, for instance, is the main form of programmed cell death reported to be involved in neurological diseases and its inhibitor, necrostatin 1, has been shown to have beneficial effects on degenerative diseases such as Huntington's disease and amyotrophic lateral sclerosis (Ofengeim et al., 2015). Recently Liang et al. (2019) reported that necrostatin 1 played a role in neuropathic pain and further observed that this small molecule decreased neuroinflammation and necrotic cell death. Moreover, it was also shown that intravenous administration of necrostatin 1 reduced amyloid-βaggregates and mitigated cell death related to the pathology of Alzheimer's disease (Yang et al., 2019). Thus, Nec-1 and necrosis inhibitors demonstrate therapeutic potential in relation to neurodegenerative diseases and chronic pain.

Apoptosis

Apoptotic cells have specific morphological characteristics such as chromatin condensation, DNA fragmentation, loss of adhesion to adjacent tissue, and specialized structures such as microvilli (Lalaoui et al., 2015). During the apoptotic process the formation of cytoplasmic vacuoles occurs, which means that the cell loses liquid and divides into small fragments, called apoptotic bodies (Hollville et al., 2019). These bodies are phagocytosed by macrophages and neighboring cells, without producing inflammation. Removal of apoptotic bodies is mediated by phosphatidylserine present in the plasma membrane (Lalaoui et al., 2015).

During the apoptotic process, phosphatidylserine is expressed on the membrane and recognized by phagocytic cell receptors. Apoptosis can be triggered by an extrinsic pathway through the activation of death receptors, located in the cell membrane or by an intrinsic (or mitochondrial) way, caused by intracellular stress (Vringer and Tait, 2019). Studies in *C. elegans* have suggested that *ced-4* activates *ced-3* and *caspase-9* composing a cell-death apparatus, whereas, in humans, *ced-4* has a homologue, apoptotic protease-activating factor 1 (Apaf-1), that binds to caspase and promotes the activation of the apoptotic process induced by caspase (Ellis and Horvitz, 1986; Suzanne and Steller, 2013). Apaf-1 is a complex known as apoptosome and its formation requires the presence of cytochrome c, released by mitochondria through apoptotic stimulation. Once the apoptosome is formed, caspase-9 cleaves and stimulates the cleavage of other caspases, such as caspase-7 and caspase-3 (Hollville et al., 2019). The level of Apaf-1 is high in mitotic cells, but decreases after neuronal differentiation, maintaining the low concentration in young post-mitotic neurons. Recent reports have shown that Apaf-1 level is increased in brain injury or in the presence of DNA damage and hypoxia (Gao et al., 2019; Hollville et al., 2019).

The autoregulation of caspases and the inactivation of proteins are crucial mechanisms for the maintenance of the cellular cytoskeleton, DNA repair, transduction signals and cell cycle control (Lalaoui et al., 2015). In this cell death process, the *ced-9* gene activation lead to the expression of a protein that is similar to Bcl-2, an inhibitor of cellular death, and has an important influence on the development and progress of this process (Edlich, 2018). Some members of this family are inhibitors of apoptosis (e.g., Bcl-2, Bcl-xL, and Mcl1) while others are activators or promoters of cell death (e.g., Bax and Bak). These members are homologous, different only in extent of the gene for Bcl-2 (Edlich, 2018). The balance between the pro and antiapoptotic classes is determinant in maintaining the viability of a cell (Hollville et al., 2019).

Members of the Bcl-2 families are present in the mitochondria (intrinsic pathway), the organelle that controls cell death (Cui and Placzek, 2018). When activated, the proapoptotic oligomers Bax and Bak are coupled to the membrane of the mitochondria (Cui and Placzek, 2018). The formation of the oligomers causes cytochrome c to be released through pores in the intramembrane space (mitochondrial outer membrane permeabilization) or through interaction with other membrane proteins (Vringer and Tait, 2019). Together with Apaf-1 and pro-caspase-9, cytochrome c forms the apoptosome, which activates the cascade of the apoptosis. Therefore, the activation of Bax or Bak results in the formation of the apoptosome that triggers cell death by the action of caspases (Pohl et al., 2018).

Caspase is inactivated by a family of apoptosis inhibitor proteins or inhibitors of apoptosis (Lalaoui et al., 2015). These proteins act by inhibiting caspase activity or by ubiquitination, degrading proteasomes (Hollville et al., 2019). During the release of cytochrome c by mitochondria, other proteins called Smac/Diablo and Omi/Htr2 are also released, which stimulate the activation of caspases by interacting with inhibitors of apoptosis and rendering them inactive (Paul et al., 2018).

Another factor capable of inducing apoptosis is the transcription factor p53. CHK and ATM protein kinases, activated by DNA damage, phosphorylate and stabilize p53 (at certain points in the cell cycle) (Akhter et al., 2015). Increasing p53 activates its own transcriptional factor which induces apoptosis because it is coupled with members of the pro-apoptotic protein family, such as Bim, Puma, Noxa, Hrk/Dp5, Bad, Bid and Bmf (known to induce mitochondrial membrane permeability indirectly by stimulating the pro-apoptotic proteins Bax and Bad) (Akhter et al., 2015; Hollville et al., 2019). P53 can regulate both cell death and cell cycle, depending on the level that is induced by DNA damage (Hollville et al., 2019).

On the other hand and to counterbalance these processes, the cells have survival pathways, one of which is mediated by the enzyme PI3K, activated by protein tyrosine kinase or by action on a receptor coupled to protein G (Zhong, 2016). PI3-phosphorylated kinase acts on the membrane phospholipid PIP2 (phosphatidylinositol 4,5-bisphosphate) to form PIP3 (phosphatidylinositol 3,4,5-triphosphate), which activates the protein kinase AKT (Rai et al., 2019). This protein is able to phosphorylate several cellular proteins for cell survival, including Bad (pro-apoptotic Bcl-2 family). Phosphorylation of Bad by Akt creates a binding site for the chaperone which leaves Bad in an inactive form, inhibiting apoptosis and promoting cell survival (Rai et al., 2019). In addition to Akt, other protein kinases act on Bad leaving it inactive, such as Ras (Zhong, 2016).

Another type of pathway that induces neuronal death is the extrinsic pathway, which is known to have death receptors. These receptors have TNF and TNF-related apoptosis-inducing ligand as their ligands and TNFR-1 and FAS/CD95 as receptors. The TNF, TNF-related apoptosis-inducing ligand or FAS

receptors are located in the cytosolic part and are stimulated by their binders. When activated, the receptors form clusters in trimer, binding to the adapter protein Fas- associated death domain, which is found in the cytoplasm (Yi et al., 2018). This protein binds to intracellular caspases such as pro-caspase-8 in the case of Fas receptor, resulting in the formation a complex called death-inducing signaling complex (Siegmund et al., 2017). This complex will result in autoclaving and activation of the other caspases, which may have a disruptive effect, such as interfering in the mitochondrial pathway, or continuing the activation of the other caspases and causing neuronal death (Siegmund et al., 2017).

Excitotoxicity

Excitotoxicity is mediated by exacerbation of the effects of the excitatory neurotransmitters, such as glutamate. This process begins with the activation of the ionotropic membrane receptor AMPA by glutamate, which allows the entry of sodium ions, leading to membrane depolarization (Goncalves-Ribeiro et al., 2019). The change in this potential leads to the activation of the Na^+/K^+-ATPase and Na^+/Ca^+-ATPase pumps, which exchange ions from the cells with the extracellular medium. In addition, this depolarization displaces the input magnesium atom that blocks the NMDA receptor, allowing calcium to enter the cell (Goncalves-Ribeiro et al., 2019).

Concomitantly, the activation of the glutamate receptor increases IP_3, responsible for opening the channels to calcium of the endoplasmic reticulum, releasing its stock of calcium (Ceprian and Fulton, 2019). Calcium also enters the cell after the depolarization of the voltage-gated calcium channel. Thus, through various mechanisms, glutamate induces increased intracellular calcium (Goncalves-Ribeiro et al., 2019).

Calcium, in turn, activates a series of proteins, such as nitric oxide synthetase, responsible for the formation of NO, a gaseous neurotransmitter that acts as a cellular flag and, in excess, can trigger cellular damage by the production of free radicals, mainly when associated with oxygen (Thornton et al., 2017). Calcium can be used as a sign of physiological or pathological changes in a cell because its concentration in the cytosol is usually low compared to that found in the extracellular fluid and in the lumen of the cytoplasmic reticulum. There are three types of calcium channels that can mediate this signaling: voltage-dependent calcium channels, IP3-activated calcium release channels and ryanodine receptors (Lin et al., 2017).

IP_3 stimulates the release of calcium from the endoplasmic reticulum, a process known as calcium-induced calcium release. However, this stimulus is inhibited when the ion concentration is sufficiently high (Goncalves-Ribeiro et al., 2019). The frequency of calcium oscillation reflects the strength of the extracellular stimulus, and can produce a frequency-dependent cellular response. Furthermore, calcium-binding proteins, such as calmodulin, are present in the cytosol of brain cells and in smooth muscle. When calmodulin is activated, it responds cooperatively to the increase in ion concentration, also serving as a regulatory subunit (Prentice et al., 2015).

Oxidative stress

Another process that can trigger cell death is oxidative stress, a state in which the production of oxidizing agents exceeds antioxidant capacities. The antioxidant defense can be separated into enzymatic and non-enzymatic. The main non-enzymatic antioxidants are glutathione, vitamin E, ascorbate; and the main enzymatic antioxidants are superoxide dismutase, catalase and glutathione peroxidase (Zhao et al., 2016). Oxidative stress generates oxidation of cellular constituents, like lipids, proteins and DNA, leading to cell death. All living organisms can be damaged by oxidation. In general, nervous tissues are more susceptible to this type of damage due to high calcium flow through the neurons; the presence of excitatory amino acids, mainly glutamate; in addition to the high rate of molecular oxygen consumption and deficiency in antioxidant defenses when compared to other tissues (Nakamura et al., 2019). Free radicals are species that have unpaired electrons and therefore react easily with other molecules. They are considered the major cause of the processes of generalized aging and decline of organic functions (Nakamura et al., 2019), and are responsible for both physical and mental aging. In the brain, they act more intensely and early, leading to problems ranging from mild memory loss to neurodegenerative diseases (Wu et al., 2019).

Mitochondria dysfunction

Cognitive decline is also associated with changes in the brain's energy metabolism. Evidence shows that mitochondrial dysfunction is present in neurodegenerative diseases as it causes a decrease in ATP production, with approximately 90% of ATP production occurring in the mitochondria. In addition, mitochondrial dysfunction results in the malfunction of enzymes in the electron transport chain, increased generation of ROS and reduced mitochondrial DNA (mtDNA) (Wu et al., 2019).

In addition to energy metabolism, mitochondria also play a key role in regulating apoptotic pathways, as stated above, maintaining redox potential and intracellular calcium homeostasis. Defects in mitochondrial dynamics and in mitochondrial quality control, as well as in mitochondrial transport and distribution in synaptic compartments have been implicated in brain aging (Raefsky and Mattson, 2017). The transport of mitochondria is essential for the survival of neurons given the need for their correct distribution in regions where there is a greater need for ATP and calcium, such as the synapse (Ashrafi et al., 2020). In the inner mitochondrial membrane there are four enzyme complexes, called I, II, III, IV, which are involved in electron transport and oxidative phosphorylation (Ashrafi et al., 2020). In addition, mitochondria are organized in a dynamic network through continuous cycles of fusion and fission, essential for mitochondrial homeostasis and adaptation to cellular needs (Islam, 2017). The fission allows new mitochondria to form that will reintegrate into the mitochondrial network after fusion, but also to eliminate dysfunctional organelles by mitophagy processes, thus allowing quality control (Islam, 2017). Changes in mitochondrial dynamics of fission and abnormal fusion directly interfere with mitochondrial function, promoting increased production of reactive oxygen species and decreased antioxidant enzymes, such as superoxide dismutase 2 (Bhatti et al., 2017; Islam, 2017). Studies conducted using animal models have shown a decrease of about 25% in mtDNA content between 6 and 26 months of age (Picca et al., 2013). However, in this study by Picca et al. (2013), an increase in the level of mitochondrial transcription factor A (TFAM) was observed, encoded by the nucleus and translocated to the mitochondria, where it regulates the transcription and replication of mtDNA. Although TFAM increased in older animals, perhaps as a compensatory response, a decrease in the association between TFAM and mtDNA was observed, supporting the association between mitochondrial dysfunction and aging.

As already mentioned, the amount of ATP produced directly interferes with synaptic plasticity since the formation and transmission of synapses requires a high energetic demand generated by mitochondria found in axonal terminals and neuronal dendrites of pre and post synaptic terminals. In presynaptic terminals, the produced ATP is used to drive the transport, the release and the endocytosis of the synaptic vesicle and to regulate ionic flows. In postsynaptic terminals, they are essential for the preservation of synaptic transmission (Chrysostomou et al., 2016; Ashrafi et al., 2020).

Ca^{2+} is known to be involved in the activation of many metabolic processes and in the regulation of muscle and nerve functions (Ashrafi et al., 2020). Furthermore, the electrochemical gradient formed between the intra and extracellular compartments allows the transduction of biochemical signals inside the cells (Ashrafi et al., 2020). Mitochondria have the role of buffering Ca^{2+} ions, maintaining neuronal polarity in presynaptic neurons after the release of synapses and in 1 postsynaptic neurons after being depolarized by glutamate activity, preventing neuronal death from excess intracellular Ca^{2+} and assist in promoting structural adaptations of dendritic spines (Raefsky and Mattson, 2017).

However, in some situations there is an exaggerated increase in the intracellular concentration of this ion, and prolonged exposure of cells to high concentrations of Ca^{2+} can cause damage by activating several pathways that indicate cell death (Ashrafi et al., 2020). In neurons, mitochondrial bioenergetics and oxidative stress, together with mitochondrial Ca^{2+} transport, form a closely connected network (Raefsky and Mattson, 2017). Deficient generation of ATP in the cell can result in failure of the Ca^{2+} pump activity in the plasma membrane and the endoplasmic reticulum with Ca^{2+} overload. In turn, oxidative stress can restrict the mitochondria's ability to generate ATP. Furthermore, the uptake of Ca^{2+} by the cell and its transport into the mitochondria can overload the mitochondrial proton circuit, which may lead to the transition of mitochondrial permeability and neuronal death induced by the energy crisis (Raefsky and Mattson, 2017).

It is worth mentioning that mitochondrial biogenesis is a complex process involving the nuclear and mitochondrial genomes, resulting in an increase in the mitochondrial mass in response to the increased energy requirement. The α co-activator of PPARγ type 1 (PGC1α) plays a central role in the regulation of mitochondrial biogenesis and the response to oxidative stress (Grimm and Eckert, 2017). In the nucleus, it interacts with the type 1 and 2 nuclear respiratory transcription factors, inducing the expression of mitochondrial genes encoded by the nucleus. In coactive mitochondria, transcription after interaction with TFAM. PGC1α activity is regulated by metabolic sensors such as adenosine monophosphate-activated kinase and sirtuins (SIRTs) (Grimm and Eckert, 2017). Sirtuins are histone deacetylases with a crucial role in regulating cell pathways involved in longevity. Regulation of SIRT activity by nicotinamide and oxidized adenine (NAD^+) dinucleotide highlights its role in metabolic homeostasis, particularly SIRT1 and SIRT3 (Egea et al., 2015). SIRT1 with cytosolic and nuclear location, is expressed in the brain, particularly in regions targeted by neurodegenerative changes related to aging such as the prefrontal cortex, hippocampus and basal ganglia, so the decrease in SIRT1 activity, documented in the brain of animals, has been linked to changes in neuronal plasticity and cognitive decline (Egea et al., 2015). SIRT3, with mitochondrial location, regulates energy metabolism and mitochondrial function, by deacetylating enzymes from metabolic pathways such as the tricarboxylic acid cycle, oxidative phosphorylation and β-oxidation (Ansari et al., 2017). By deacetylating and activating the antioxidant enzyme superoxide dismutase, SIRT3 has a protective action in oxidative stress conditions (Ansari et al., 2017). Thus, increased SIRT3 expression protects neuronal cells from oxidative damage induced by the activation of microglia and mitochondria-dependent apoptosis (Jiang et al., 2017). Neuropathological assessment of the brain of Alzheimer's patients showed a significant decrease in SIRT3 expression and content in the cerebral cortex, which was related to a decrease in the expression of mitochondrial genes, a decrease in oxygen consumption and an increase in the ROS formation (Lee et al., 2018). All these changes produced by mitochondrial dysfunction generate an environment of oxidative stress and neuroinflammation in aging, altering the neurotrophic phenotype of astrocytes to a scenario in which there is disruption of the metabolic support provided by astrocytes to neurons and which is essential for cognitive function 8 (Tsai et al., 2016).

Autophagic dysfunction

Autophagy can generally be defined as a catabolic process of degradation and recycling, responsible for removing and digesting malformed or damaged cellular contents, organelles and proteins (Wang et al., 2019). This mechanism is dependent on lysosomal machinery, and has a high level of conservation among eukaryotes, which is easily explained, since its function is essential to protect and adapt the organism in a stressful situation, until the cell is able to return to its homeostasis state. In addition, basal autophagy is extremely necessary as a cleaning route under normal nutrient supply conditions, and not just under pathological conditions. Above all, to protect cells from toxic effects of dysfunctional proteins that cannot be removed via cell division (Wang et al., 2019).

Autophagy is also the most used pathway for the degradation of damaged intracellular organelles and aggregated or malformed proteins (Wang et al., 2019). Since the presence of protein aggregates is a common feature and is present in most neurodegenerative diseases, including Alzheimer's (beta amyloid and Tau plaques), Parkinson's (alpha synuclein) and Huntington's (huntingtin) (Frake et al., 2015), autophagy is expected to play a crucial role in removing these toxic aggregates, by decreasing harmful effects and protecting the cell (Wang et al., 2019).

In addition, autophagy is able to protect against infectious diseases and promote immunity, being the main form of innate immunity against exogenous invaders (Rubinsztein et al., 2015). Both in infectious diseases and in inflammation observed in neurodegenerative disorders, it was found that stimulation of autophagy had protective effects in preclinical trials (Rubinsztein et al., 2015). There are studies with several animal models demonstrating that when modulating autophagy via the mTOR- dependent pathway (mammalian target of rapamycin) there is an increase in the clearance of toxic proteins (Menzies et al., 2017). In addition, the inhibition of autophagy was able to increase the toxicity of these proteins and lead to a considerable increase in aggregates (Frake et al., 2015). This modulation has been done in studies with the drug rapamycin, and represents a promising strategy in diseases with protein accumulation (Frake et al., 2015; Menzies et al., 2017).

There are three different mechanisms by which autophagy can process cellular structures: macroautophagy, microautophagy and chaperone-mediated autophagy (Frake et al., 2015). Macroautophagy is a conserved pathway in mammals and the most recurrent process in autophagic events. It consists of transporting substrates to lysosomes through the formation of vesicles created from an isolated membrane, forming a double membrane structure called an autophagosome, which acts as an "insulating" structure of proteins and organelles. For the degradation of these substrates to occur, the autophagosome undergoes a fusion with the lysosome, thus forming an autolysosome, in which later this material will break down and be recycled by lysosomal hydrolases (Menzies et al., 2017). Autophagosome formation is highly regulated by the ordered assembly of a family of proteins called ATG (AuTophaGy-related) (Menzies et al., 2017), with the Beclin1/Vps34 complex being the essential nucleus for the formation of the autophagosome, and may both stimulate and suppress the beginning of the autophagic process, participating in different steps, including autophagosome biosynthesis and maturation (Pickford et al., 2008).

In microautophagy unlike macroautophagy, there is

no formation of the intermediate structure of the autophagosome, consisting of a process of invagination or direct protrusion of the lysosomal membrane (Cuervo and Wong, 2014), whereby substrates are degraded by lysosomal enzymes, which can be both selective and non-selective. This process and its mechanisms in pathologies is still poorly understood, in part due to the difficulty of analysis.

Chaperone-mediated autophagy, on the other hand, consists of a highly specific pathway (Cuervo and Wong, 2014). The substrates to be degraded by this route are marked by the motif containing the pentapeptide KFERQ (Lys-Phe-Glu-Arg-Gln), which is recognized by a complex formed with the cytosolic heat shock protein (HSPA8/HSC70), which transports the substrate to the lysosome membrane where it unfolds and binds to monomers of the LAMP2A receptor (protein associated with the lysosome membrane) (Cuervo and Wong, 2014).

Beclin1 (also known as Atg6) is an autophagic protein that is part of the PI3K kinase complex and plays an essential role in the formation of autophagosomes. A reduction in this protein was observed in the brains of patients with Alzheimer's disease (Furuya et al., 2005). Pickford et al. (2008) showed the essential role of Beclin1 in autophagy, since the knockout of the Beclin1 gene in PDAPP mice dramatically compromised the process. There was an increase in the accumulation of intraneuronal beta amyloid, decreased neuronal autophagy, neurodegeneration, lysosomal rupture and microglial alterations, indicating neuronal injury. It was also found in that same study that Beclin1 overexpression reduced levels of both intracellular and extracellular amyloid-β.

According to Menzies et al. (2017), although there is growing evidence of the physiological importance of autophagy in normal neuronal physiology, the clinical pathological manifestation of most neurodegenerative diseases is late, so it is possible that small changes in the autophagic machinery and consequent recycling of the aggregates have cumulative effects that will manifest themselves only later in life. In addition, autophagy consists of an extremely dynamic and highly regulated process, making the identification of the complex occurrence in initial steps with less biological repercussion. Taking all of these studies into account, the present set of findings suggests that the decrease in autophagic events or their impairment may contribute to Alzheimer's pathology. It is essential that the entire autophagic pathway, from the induction stage to the subsequent stages of maturation and purification, are highly regulated. It is suggested that the pathology characterized by beta amyloid accumulation occurs partly through impaired autophagy, an essential pathway for the degradation of cytotoxic protein aggregates (Menzies et al., 2017). Based on the data found in these studies, an attempt has been made to understand the relationship between the autophagy process and the mechanisms by which this phenomenon occurs in the context of neuroprotection against neurodegenerative diseases. Autophagy may be a relevant therapeutic target for these disorders.

Cell senescence, neurodegeneration and neuroprotection

Cell senescence is a fundamental, multi-faceted aging mechanism defined by irreversible cell cycle arrest determined by several mechanisms, such as telomere shortening, activation of oncogenes, oxidative stress and cell-to-cell fusion (Biran et al., 2017; Childs et al., 2017). In this situation, cells produce SASPs that include proinflammatory agents like cytokines and chemokines, growth factors and proteases. The release of these factors leads to the formation of irregular nuclei and pleomorphic mitochondria, a reduction in endoplasmic reticulum and distortion of the Golgi apparatus leading to dysfunction of many cell types (Wang et al., 2019).

Secretion of SASPs produces potent effects in neighboring cells changing the local tissue. The main reported beneficial effect of SASPs (chemokines and cytokines) that are secreted by senescent cells is the ability to recruit natural killers for the clearance of tumor cells. At the same time, the main detrimental effects promoted by SASPs are the interruption of the structure and function of normal tissues, the induction of transitions between normal epithelial cells and pre-malignant cells and stimulation of pre-malignant but non-aggressive cancer cells to move around and go inside the basal membrane (Chinta et al., 2015).

Some stressors are classically linked to cell senescence. Although not fully understood, these stressors trigger all the mechanisms described above and create a suitable neuroinflammatory environment for cancers and neurodegeneration. The phosphorylation of tau protein, for instance, has been linked to the release of SASPs and promotion of toxicity in central nervous system cells (Mendelsohn and Larrick, 2018). Amyloid-β plaques, a neuropathological marker of Alzheimer's disease, are also being related to cell senescence in the brain, causing oligodendrocyte progenitor cells to release SASPs and create a destructive environment (Zhang et al., 2019). In agreement with this, some environmental agents like pesticides (paraquat) can also induce cell senescence and trigger α- synuclein phosphorylation, increasing the probability of Parkinson's disease (Chinta et al., 2018). With all this information, it is natural to think about the development of senolytic drugs and strategies to prevent or treat cell senescence and decrease the increasing incidence of the related devastating neurodegenerative diseases.

A number of fundamental studies are, therefore, being conducted to better understand the mechanisms of cell senescence and advance senolytic treatments. Hydrogen peroxide (H_2O_2) is one example of a stressor that induces the release of ROS and triggers cell senescence by oxidative stress induction. Depending on the stressor concentration, cells can present significant damage leading to necrosis, or cumulative damage that brings the beginning of apoptotic mechanisms or cell senescence and the development of diseases (de Magalhaes and Passos, 2018). Even the presence of few senescent cells may lead to cellular and organ dysfunction, impairment of tissue renewal and the development of an aging phenotype (de Magalhaes and Passos, 2018).

However, in some species (spiny mice and rabbits, for instance), there are mechanisms of cell protection that are linked to regeneration that are not found in other species (like other mice and rats). In these species, there is an increase in the resistance limit for mitochondria in response to H_2O_2 stress that increases regenerative ability (Saxena et al., 2019). This mechanism may have implications for healing and overcoming cell senescence and for similar mechanisms that could be explored to increase neuroprotection.

There is increasing evidence for protective products that are being considered as potential senolytic agents. These include the well-known substances quercetin, piperlongumine and curcumin that are already commonly taken as antioxidants and neuroprotectives, and are now being taken as natural senolytics that can extend healthspan (Liang et al., 2019). Many studies have addressed *in vitro* cell senescence caused by stressors and the effects of senolytics, but the *in vivo* evidence comes only from animal studies with limited translational correlation to human beings, mainly because of the differences between rodent and human biology (Kirkland and Tchkonia, 2017). The long-term effects of these products, therefore, still needs to be investigated, as not all senescent cells are bad and need to be eliminated (wound healing, for instance, involves the activation of senescent cells). Strategies that eliminate senescent cell inductors in a

balanced way may be the key to healthy aging and the "super-agers" phenomenon (people aged over 85, with no cognitive dysfunction, cancer or cardiopulmonary disease), beyond the general genetic heritage that supports the hypothesis to explain the extended healthspan in this population (Halaschek-Wiener et al., 2018).

Strategies to maintain resistance or resilience of neurons and astrocytes

Several pharmacological and non-pharmacological strategies are currently being developed to increase neuroplasticity, and promote neuroprotection or even neurogenesis. In the last five years, our research team has shown that particular lifestyles are definitely neuroprotective and adopting these can change the course of the aging process. It has been shown that chronic treatment with microdose lithium carbonate (Li_2CO_3) can reduce neuronal loss in the hippocampus and increase neuronal density in the pre-frontal cortex of transgenic mice for Alzheimer's disease, as well as increase the density of BDNF in the same area (Nunes et al., 2015). Also, in organotypic hippocampal tissue from old senescence-accelerated mouse prone 8 (SAMP-8) a significant reduction in nuclear factor-kappa B activation and release of proinflammatory cytokines was observed after microdose Li_2CO_3 treatment, together with an increase in the density of the anti-inflammatory cytokine IL-10. As a proof-of-principle, many short clinical studies were done, suggesting the beneficial effects of microdose lithium in patients with mild cognitive impairment (MCI) or diagnosed with Alzheimer's disease (Rybakowski, 2018). In a study with 61 older adults with MCI, for example, treatment with low concentrations of Li_2CO_3 for 24 consecutive months promoted a better performance in memory and attention tasks, when compared to placebo treated age-matched individuals (Forlenza et al., 2019). Also, considering that Alzheimer's disease can be an early source of morbidity for individuals with Down syndrome, a recent medical hypothesis points to a real possibility of the benefits of microdose lithium to prevent early dementia in this population (Priebe and Kanzawa, 2020).

Still focusing on the suppression of neuroinflammation and oxidative stress, studies with humans and rodents show that polyphenols can be used to avoid inflammation and cellular apoptosis (Spagnuolo et al., 2016). One example is, pomegranate, a fruit with high levels of polyphenols in the pulp and in the peel (Yang et al., 2016). Our group showed that mice submitted to a neurodegenerative model with the infusion of amyloid-beta peptide (1–42) and then treated with pomegranate peel extract presented increases in BDNF levels in the hippocampus and a reduction in senile plaque density, which contributed to improved spatial memory (Morzelle et al., 2016). It is believed that the neuroprotective effect of pomegranate is related to the production of the metabolite urolithin, as it has already been shown that this compound can inhibit the formation of senile plaques and prevent neurotoxicity (Yuan et al., 2016). Another potent polyphenol that has a reported neuroprotective action is resveratrol. In a controlled trial with 60 old people (60–79 years old), treatment with this compound promoted preservation of verbal memory and improvements in memory related to the recognition of patterns (Huhn et al., 2018).

As discussed above, an increased BDNF level is a sign of neuroprotection, as the activation of tropomyosin receptor kinase B receptors leads to the activation of the PI3K/Akt neuroprotective antiapoptotic pathway (Kowianski et al., 2018). Physical exercise is a well-known strategy that increases BDNF and other hormones like irisin, leading to significant improvements in cognitive function, both in animals and humans (de Meireles et al., 2019; Chen and Gan, 2019). Moderate physical activity for 11 weeks, for instance, improved the cognitive ability of less-responsive rats to a memory task (in an active avoidance apparatus) (Albuquerque et al., 2016). In addition to improving cognitive ability, moderate physical activity promoted neurogenesis, prevented neuronal death, and induced neuronal differentiation, unlike intense physical activity that did not produce similar effects (So et al., 2017).

Another benefit of moderate physical activity is the release of irisin, a hormone released into the bloodstream through activation of the Fndc5 gene by the PGC-1α gene transcription co-activator (Ruth, 2012). Irisin also promoted synaptic function improvement and prevented cognitive decline in transgenic Alzheimer's disease-like mice (Lourenco et al., 2019). Similar effects have also been observed in animals with ischemic stroke and increased activation of the PI3K/Akt and ERK 1/2 signaling pathways after administration of irisin (Li et al., 2017).

Both physical activity and environmental enrichment have been seen as means of improving memory and learning as well as increasing hippocampal neurogenesis (Sakalem et al., 2017), leading to the construction of a cognitive reserve. In a study recently published by our group, we demonstrated that an enriched environment promoted memory retention in a transgenic mice model of Alzheimer's disease (Balthazar et al., 2018). In addition, it is has already been shown that environmental improvement can promote a reduction in the pro-inflammatory cytokine IL-1β and an increase in astrocytes (Goncalves et al., 2018). In humans, it seems that physical exercise has benefits when undertaken over a long-time period. Exercises for 12 or 16 weeks, for example, did not significantly change the parameters related to improvements in cognition like increased cerebral blood flow or growth factors (as BDNF) (van der Kleij et al., 2018; Marston et al., 2019). However, individuals who have greater activity for a longer period (1 year) have been shown to have a higher hippocampal volume (Clemenson et al., 2015). These data demonstrate that improvements in cognitive performance and neurogenesis can be related to a more active stimulating life. These studies clearly show that lifestyle, and not only pharmacological treatments, is important in the promotion of neuroprotection and neurogenesis. Therefore, studies that analyze both pharmacological and non-pharmacological strategies are extremely important in the production of reliable results.

Conclusion

During the aging process, neuroplasticity and memory are subjected to environmental conditions that influence individuals' genetic profiles and may lead to the development of a cognitive reserve as well as better all-round health in older adults. Neurodegeneration can be modulated by alterations in cell senescence, which can decrease neuronal and glial cell populations, leading to dysfunction of the central nervous system. However, a healthy life style can help to maintain the neuroprotective mechanisms that work against the cell death processes involved in neurodegenerative diseases. More studies are needed, particularly *in vivo* studies and studies focused on human cells, to clarify the role of cell senescence in neuroprotection during aging, and to facilitate the development of senolytic drugs, as well as to provide further scientific evidence on the role of physical exercise, better nutrition and environmental enrichment in improving quality of life and increasing healthspan.

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