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# Implication of Oxidative Stress, Aging, and Inflammatory Processes in Neurodegenerative Diseases: Growth Factors as Therapeutic Approach

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## Oxidative Stress and Neurodegeneration

Oxidative stress (OS) is defined as the imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense system. Living organisms produce ROS from molecular oxygen as a consequence of normal cellular metabolism. In order to prevent damage, cells have an antioxidant defense system constituted by an enzymatic component (including catalases, superoxide dismutases, etc.) and nonenzymatic antioxidants component (glutathione, α-tocopherol, ascorbic acid, etc.). When the levels of ROS exceed cell capacity, it can cause damage in cellular components such as carbohydrates, nucleic acids, lipids, and proteins, thus altering their function. Whenever this imbalance occurs within the central nervous system, it can lead to the development of the neurodegenerative disorders.

Neurodegenerative diseases are characterized by the loss of neuronal cells and, in most cases, by the aggregates of proteins that form intracytoplasmic and intranuclear inclusions in neurons and glial cells. Data on the literature show that there are two possible mechanisms involved in most of neurodegenerative diseases: (1) mutations and/or aggregation of characteristic proteins of each disease such as α-synuclein in Parkinson's disease (PD) or beta-amyloid peptide in Alzheimer's disease (AD) and (2) dysfunction of mitochondrial energy metabolism in neurons. In this section, we will focus on this last one.

In the CNS, mitochondria are in charge of the production of needed energy to drive most cellular reactions through oxidation of glucose under aerobic conditions, ending up in the electron transport chain (ETC) [1]. A loss of mitochondrial function at this level is associated with neurodegenerative processes. Consequently, in view of the susceptibility of the ETC to oxidative damage, loss of ETC activity, due to an increment of ROS levels, has been proposed to be a plausible mechanism for the neuronal cell death associated with PD, AD, and other neurodegenerative disorders [2].

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Furthermore, the "beta-amyloid ($A_\beta$) cascade hypothesis" that dominated the field of AD research for the past decades has been challenged, and a new "mitochondrial cascade hypothesis" has been proposed. The mitochondrial cascade hypothesis states that in sporadic, late-onset AD, loss of mitochondrial function associated with age affects the expression and the processing of APP, initiating $A_\beta$ accumulation [3]. It is known that not only the partial reduction of $O_2$ increases superoxide radical ($O_2^-$) in normal conditions but also complex I participates [4, 5]. Complex I (CI or NADH:ubiquinone oxidoreductase) is the largest ETC enzyme, containing 44 subunits and the main contributor to ROS production. Regarding this, many authors have described that complex I is disturbed in AD and PD [6, 7], increasing even more ROS levels [8]. Moreover, Schapira et al. [9] have reported a decreased activity of complex I in the substantia nigra of nine postmortem patients with PD. Giachin et al. [5] reviewed that neuronal cells are particularly susceptible to ROS-induced damage because they rely mainly on oxidative metabolism for ATP generation, contrary to glial cells, which are highly glycolytic. This overproduction of ROS not only increases OS able to oxidize biomolecules [10–12] but also leads to the activation of poly(ADP-ribose) polymerase (PARP), responsible for the repair of the DNA using NADH, inhibiting the glycolytic pathway caused by a reduction in NAD+ content. This leads to the subsequent compromise of the respiration at complex I where NADH is a key cofactor [13, 14].

Mitochondrial complex IV (cytochrome c oxidase) is also associated with development of neurodegeneration, in particular AD. Some authors described decreased levels of cytochrome c oxidase in neuronal mitochondria of AD postmortem brain patients [10]**.** Moreover, it is also known that $A_\beta$ specifically inhibit cytochrome c oxidase. This decrease could also be able to rise ROS levels [8, 12], leading to neuronal death.

In conclusion, although neurodegeneration is associated with multiple etiologies and pathophysiologic mechanisms, oxidative stress appears as a major part of the pathophysiologic process. Here, neuronal loss is caused by mitochondrial dysfunction and oxidative stress, among other factors. Mitochondrial function declines with age, with a concomitant increase of OS.

## Neuroinflammation and Neurodegenerative Diseases

The central nervous system (CNS) presents a unique microenvironment given to the isolation due to the blood-brain barrier (BBB), which separates the brain from the periphery. BBB maintains chemical balance within the CNS to support neuronal function as well as limits the entrance of invading microorganisms [15]. Moreover, glial cells – microglia and astrocytes – constitute the neuroimmune system monitoring the CNS. These cells participate in various processes, such as phagocytosis, steroid and growth factor release, free radical reduction, and cellular repair, in both healthy and diseased brain [16–19]. Therefore, due to these peculiar characteristics, the CNS could be considered as an immunologically privileged organ.

In the last decades, the average lifespan has increased due to the improvement of medical care and hygienic conditions. This fact comes together with an increment in the incidence of age-related diseases. Alzheimer's disease is the most common neurodegenerative disorder, which is characterized by the presence of extracellular β-amyloid (Aβ) deposits and intracellular neurofibrillary tangles composed of phosphorylated protein Tau, resulting eventually in the characteristic memory loss [20]. The second most common neurodegenerative disease is PD, which is characterized by the aggregation of α-synuclein into Lewy bodies and Lewy neurites and the specific loss of dopaminergic neurons in the *substantia nigra pars compacta*, resulting in the exhibition of tremors, stooped posture, and dementia in some cases [21]. Regarding Huntington's disease (HD), it is an autosomal dominant disease caused by a mutation in the huntingtin gene. Its manifestations include chorea and cognitive and behavioral decline [22]**.**

Neurodegenerative diseases are accompanied by chronic inflammation, where the neuroimmune cells, mainly microglial cells, activate and adopt pro-inflammatory states (known as M1 phenotype).

This state is characterized by the production of pro-inflammatory cytokines, which amplify the inflammatory response by recruiting and activating more microglial cells as well as promoting their proliferation. Many of these cytokines such as tumor necrosis factor alpha (TNFα) and interleukin 1 beta (IL-1β) have been shown to lead to neuronal death both in vivo and in vitro [23, 24]. TNFα can induce cell death through (i) apoptosis via activation of caspase-8; (ii) necrosis via activation of receptor-interacting protein 1 (RIP1), receptor-interacting protein 3 (RIP3), and mixed lineage kinase domain-like protein (MLKL); and (iii) inflammation via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Moreover, M1 microglia characteristically expresses inducible NO synthase (iNOS), which produces high levels of NO continuously. These high levels of NO cause neuronal death by inhibition of mitochondrial cytochrome oxidase in neurons, leading to neuronal depolarization [25].

It is worth highlighting that, though inflammation contributes to the development and maintenance of degenerative diseases, it is not an initiation factor. In fact, an inflammatory response necessarily has to occur in order to guarantee the removal of harmful agents and repair of injuries. In this acute inflammation, microglial cells adopt an anti-inflammatory phenotype (termed M2), characterized by the release of anti-inflammatory cytokines such as tumor growth factor beta (TGF- $\beta$) and interleukin 10 (IL-10) and the expression of arginase-1, which inhibit the release of pro-inflammatory factors [26]. Consequently, we can conclude that it is the imbalance between the pro- and anti-inflammatory molecules secreted by microglial cells that defines whether the immune response will be beneficial or detrimental for the CNS.

## Aging and Neurological Dysfunctions

The twentieth century was the century of population growth, and the twenty-first century will go into the history books as the century of aging. Global aging has been accelerating since 1969 when there were 550 million older adults, with a population of 1250 million in the year 2025 [27]. Only in the United States, the number of adults over the age of 64 will grow to 70 million by the year 2030, and they become the fastest-growing segment of the population [28]. With advanced age comes a decline in sensorimotor control and functioning and cognitive and learning impairment. As a consequence, aging is the major risk factor for the development of human neurodegenerative process such as Alzheimer's, Huntington's, and Parkinson's diseases [29].

For instance, dysfunctions in fine motor control, locomotion, and balance affect the ability of older adults to perform activities of daily living and maintain their independence. The causes of these motor deficits are multifactorial, with central nervous declines and changes in sensory receptors, muscles, and peripheral nerves playing a role [30]. As a result, aging drives changes in brain structural regions: an age-related degeneration of the cerebellum [31], which may contribute to deficits in multi-joint coordination and postural stability in older adults [30] and a reduced volume of gray matter, often present with greater ventricular and cerebrospinal fluid volume [32, 33]. Furthermore, the prefrontal cortex is particularly susceptible to gray matter atrophy [34], and the differential thickness in prefrontal and parietal cortices may be relevant to motor age performance deficits in old age because motor control is more dependent on these brain regions in older adults. In 2004, the group of Salat found significant age effects in both the primary motor cortex, contributes to the movement slowing seen with age, and the somatosensory cortex, increased falls, poor balance, and increased reliance on visual feedback for motor performance in older adults, and they marked a potential vulnerability of these regions of the brain to age-related atrophy [35].

Aging also drives changes in neuronal and cognitive function. The hippocampus, a brain region subserving roles of spatial and episodic memory and learning, is sensitive to the detrimental effects of aging at morphological and molecular levels. With advancing age, synapses

in various hippocampal subfields exhibit impaired long-term potentiation [36], an electrophysiological correlate of learning and memory. At the molecular level, immediate early genes are among the synaptic plasticity genes that are both induced by long-term potentiation and downregulated in the aging brain [37]. Besides, age-related cognitive impairment is associated with a specific set of synaptic plasticity proteins with roles in structural and functional synaptic systems [38]. Deak and Sonntag observed that an evolving area of research in brain aging is focused on the balance between excitatory and inhibitory synaptic systems [39, 40], especially in a reduction of synaptic markers [41].

Despite brain structural effects, there are also prominent differences in brain neurochemistry of older adults. For example, dopaminergic system has been most widely studied and appears to have dramatic effects. There is a significant decline in dopamine transmission levels – reduction of neurotransmitters, receptors, and transporters – and due to this general decrease in dopamine levels, the aging brain is often considered to be located in the preclinical continuum of Parkinson's disease. Dopamine also plays a significant role in higher cognitive functions such as working memory [42], which is very important for motor skill acquisition [43]. So, these cognitive impairments associated with dopaminergic degeneration may indirectly contribute to age-related motor dysfunction.

In addition to a dopaminergic decline, a cholinergic reduction with age has been found in the medial forebrain and hippocampus [44]. Several studies have associated cholinergic decline in hippocampus with Alzheimer dementia, which involves severe deficits in learning and memory. Also, there is a serotonergic decline in the cingulate cortex and putamen [45] which has been related to cognitive deficits ([46] and motor dysfunctions [47]. There is a significant reduction associated with age of norepinephrine levels due to a loss of neurons in the locus coeruleus [48].

Aging and age-related disease are a mounting challenge for individuals, for families, and for social, economic, and healthcare systems. Implementation of preventive health strategies to decrease, delay, or prevent these affections may increase health expectancy and allow people to age gracefully and mantain an independent life style, without disability, for as long as possible [49].

## Estrogen as Neuromodulators and Neuroprotectors

Estrogen is a potent steroid of both gonadal and neuronal origin implicated in reproductive functions as well as in neuromodulatory and neuroprotective actions on the central nervous system [50, 51]. Local synthesis of this molecule in the central nervous system may prevent or reduce neurodegeneration. Steroids modulate the expression of neuropeptides such as neuropeptide Y (NPY), galanin, and β-endorphin. NPY regulates the reproductive cycle, and estradiol administration has been shown to decrease NPY expression in the arcuate nucleus [52, 53], whereas the absence of this hormone results in an increase of NPY mRNA levels [54]. β-Endorphin is another peptide involved in energy and reproductive homeostasis. Estradiol stimulates the activity of pro-opiomelanocortin (POMC) cells, increases the levels of POMC mRNA, and even increases the number of these cells [53, 55, 56].

Moreover, estrogens participate in a series of protective function processes. One example is the promotion of cell survival and synaptic plasticity. In vitro studies have shown that the addition of 17β-estradiol to primary cultures of various neuronal populations (hypothalamic, neocortical, hippocampal, and amygdala) increased viability, survival, and differentiation [42, 57–59]. This molecule also regulates the expression and the action of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) and their receptors (trk, p74) [60]. Neurotrophins are a family of proteins that favor the survival, development, and function of neurons, and estrogens can interact with them by convergence (e.g., sharing the same signaling cascade, acting synergistically), by inducing their expression through estrogen response elements, or

by dependence, where the two components are needed to obtain a complete effect [61, 62]. Estrogens exert their functions via the classical nuclear receptors, regulating transcription factors that control the expression of estrogen-sensitive genes and membrane receptors (independent of transcriptional activation), which elicit faster responses than genomic effects. The most well-characterized nuclear receptors are estrogen receptor α (ERα) and estrogen receptor β (ERβ) [61], and among the membrane receptors is G-protein-coupled receptor 30 (GPR30) which, according to in vitro studies in cortical neurons, is involved in neuroprotection against oxidative stress [63].

The preoptic area, the hypothalamus, and the amygdala are the regions with the highest expression of ERs, although expression of these is also observed in regions of the cortex, hippocampus, and midbrain. Although ERα is the subtype with the highest expression in most regions, there are areas such as the mesencephalon, where ERβ predominates [64].

Estrogens can also prevent neuronal dysfunction by alterations in the levels of neurotransmitters, their receptors, and second messengers, through estrogen-binding sites in the plasma membrane [65]. For example, estradiol could regulate the release and uptake of dopamine by decreasing the affinity of dopamine receptors in order to protect the nigrostriatal system from excitotoxicity [66–68].

Several studies evidence the neuroprotective effects of estrogens in neurodegenerative diseases and traumatic damage. In Alzheimer's disease, estradiol could affect β-amyloid aggregation by regulating its metabolism and apolipoprotein E (ApoE) expression [69, 70]. In addition, this hormone could be involved in the regulation of cholinergic and serotonergic neurotransmissions, thus reducing the cognitive and affective symptoms of the disease.

Estradiol has anti-inflammatory effects in the brain that are mediated, at least in part, by a reduction of reactive gliosis [60, 71] and contributing to neuronal regeneration [72–74].

As it has already discussed, there are numerous neuroprotective actions of estrogens that have direct relevance to neurodegenerative diseases. Despite these actions, the promise of estrogen-based therapies for reducing the risk for neurodegeneration remains to be fulfilled. The application of estradiol as a neuroprotectant in humans presents numerous limitations, mainly due to the endocrine actions of the molecule on peripheral tissues, including estrogen dependent tumors. Therefore, as ongoing research continues to address these crucial and immediate concerns, an emerging area of investigation is the development of natural and synthetic hormone mimetics that will preferentially activate estrogen neuroprotective mechanisms while minimizing adverse effects in other tissues.

## Neurological Dysfunctions and Brain's Growth Factors

Neurotrophic factors (NTFs) are diffusible peptides secreted from neurons and neuron-supporting cells. They serve as growth factors for the development, maintenance, repair, and survival of specific neuronal populations, and they act via retrograde signaling from target neurons by paracrine and autocrine mechanisms [75, 76]. NTFs have different functions depending on the stage of life. During development they contribute to the formation of synaptic network [77, 78], neuronal survival, and axonal growth [79, 81]**.** In adulthood they are associated with neuronal survival and maintenance of different neural phenotypes [80].

An additional basic activity of many growth factors in the nervous system is influencing on the proliferation, migration, and differentiation of stem cells in the developing and adult nervous system [81, 82]. These basic properties are also employed by the nervous system in the case of disease and injury and thus constitute a powerful endogenous repair and maintenance system. NTFs act together in a coordination mode, so that any alteration on their local synthesis and/or transport caused by traumas, pathologies, or even aging could lead to neuronal death. Loss or dysregulation of endogenous trophic factors could contribute to the development of neurodegenerative diseases.

Neurotrophic factors are classified in superfamilies, according to their structure or function, as follows: (i) nerve growth factor (NGF) superfamily; (ii) transforming growth factor (TGF)-beta superfamily, consisting of the glial cell line-derived neurotrophic factor (GDNF) family, the TGF-beta family, and the bone morphogenetic protein (BMP) family; (iii) neurokine or neuropoietin superfamily; and (iv) non-neuronal growth factors that include IGF-1 and acidic and basic fibroblast growth factors (aFGF and bFGF, respectively). In the last decade, there have been described two new NTFs that cannot be included in the previous classification. They are cerebral dopamine neurotrophic factor (CDNF) and mesencephalic astrocyte-derived neurotrophic factor MANF [83]. Both are structurally and functionally clearly distinct from the classical, target-derived neurotrophic factors (NTFs) that are solely secreted proteins [82].

The potential for a therapeutic application of these factors has been realized early on, and the last two decades have seen several approaches to exploit this potential in different neurological disorders. The next section summarizes the current data on NTFs and their potentiality as therapeutic agents for neurodegenerative diseases.

## NTFs and Neurodegenerative Diseases: Evidences and Perspectives

There is clear evidence that neurodegenerative diseases course with impairment levels of neurotrophic factors or their receptors. For example, in PD there is a small decrease in staining density for BDNF and dopaminergic projection areas; GDNF levels are reduced (about 20%) in the substantia nigra pars compacta (SNpc) from PD patients compared with age-matched controls. The researchers also found that ciliary neurotrophic factor (CNTF) decreased as compared with age-matched controls, 11.1%/neuron and 9%/neuropil, and markedly increased levels of tumor necrosis factor and interleukin 6 (IL-6) in the nigrostriatal DA regions of PD patient [84].

Respect to the other major neurodegenerative disease, Alzheimer's disease (AD), it had been described increases in NGF and decreases in BDNF in hippocampal and neocortical regions. It was also observed decreases in tropomyosin receptor kinase A (TrkA) in the cortex and nucleus basalis in advanced AD [85, 86].

The well-documented role for neurotrophic factors to prevent cell death and to maintain cellular function has led scientists to investigate their use as therapeutic drugs and benefits. In the last years, there have been numerous preclinical and clinical studies involving treatment of neurodegenerative diseases with NTFs (for review see [84, 87–89]).

Despite the evident heterogeneity, the results from the reviewed studies can aid in conducting human trials applying NTFs. The reviews mentioned highlight that targeted local deliveries of NTFs led to favorable safety and efficacy outcomes when administration regimens successfully target a degenerated neuronal population. The previous works suggest that the application of NTFs is generally safe and well tolerated when administered locally.

In conclusion the strong potential of NTFs to exert pro-survival and pro-functional responses in neurons of the peripheral and central nervous system makes them good target candidates for treatment of a multitude of neurodegenerative disorders. However significant problems need to be overcome before translating the potential of neurotrophic factors into the therapeutic area.

## Insulin-Like Growth Factor-1 as a Therapeutic Factor

As we previously mentioned, neurotrophic factors that prevent degeneration and restore the function of the remaining neuronal populations are currently of increasing clinical interest as targets of therapeutic possibility in the treatment of neurodegenerative diseases. One of these neurotrophic factors is IGF-1. It is known, in rats, that tissue level of IGF-1 and its receptor decrease significantly in the hippocampus and cortical

layers II/III and V/VI throughout life [90]. It is also known that in situations of cytotoxic hippocampal damage, the microglia of this region substantially increases the production of IGF-1 and IGF-binding protein 2, suggesting a neuroprotective role of these molecules in the central nervous system [91].

It has also been documented that IGF-1 protects hippocampal neurons from the toxic effects of amyloid peptides [92] and that treatment with IGF-1 in mice overexpressing a mutant Aβ-amyloid peptide markedly reduces the peptide levels and improves their cognitive ability [93]. In vitro studies have shown that IGF-1 increases the cell survival of primary cultures and hypothalamic neurons [94] and stimulates the differentiation of rat dopaminergic mesencephalic neurons [95]. Also, IGF-1 modulates the inflammatory response of astrocyte cultures treated with lipopolysaccharide (LPS) [96].

There are mechanisms that suggest neuroinflammation is harmful, at least partially, because it avoids the neuroprotective action of IGF-1 [97]. Moreover, a protective effect of IGF-1 on hypothalamic cells exposed to glutathione-depleting agents has also been described [98], as well as in human, dopaminergic culture cells exposed to the salsolinol toxin and in human and murine neuronal cultures exposed to high doses of dopamine [99]. Recently, Rodriguez-Perez et al. [100] demonstrated that IGF-1 participates together with the local renin-angiotensin system to inhibit or activate neuroinflammation (M1-M2 phenotype transition), oxidative stress, and dopaminergic degeneration induced by $MPP^+$ neurotoxin.

Short-term studies of our group revealed that gene therapy with IGF-1 in the senile female rats with DA neurodegeneration is highly effective to restore hypothalamic DA neuronal function, thus correcting the chronic hyperprolactinemia associated with the dysfunction of tuberoinfundibular dopaminergic neurons (TIDA) in senile rats [101]. Also, ICV gene therapy with IGF-1 partially but significantly restores motor performance in this model of spontaneous TIDA neurodegeneration in senile animals [102, 103].

Among the possible effector fields of IGF-1 on synaptic plasticity and hippocampus, it is known that within a glutamatergic synapse, there is a positive effect of IGF-1 on synaptic transmission and consequently a prevention of cognitive deterioration. IGF-1 (as well as ghrelin, GLP-1, and insulin) is reported to be one of the molecules that stimulate glucose metabolism, providing energy for the biosynthesis of neurotransmitters. In this way, it would facilitate hippocampal circuits in terms of plasticity and synaptic structure, as well as participating in neurogenic aspects modifying learning, memory, and cognitive functionality [104]. This indirect mechanism of action would be mediated by the IGF-1 signal receptor that leads to voltage-dependent calcium channel phosphorylation, causing increased calcium and release of neurotransmitters that would facilitate synaptic conduction [105].

Currently, it is unknown whether IGF-1 exerts a direct effect on the mobilization of synaptic vesicles and the core complex of soluble NSF attachment protein (SNARE) proteins during neurotransmitter exocytosis. Interestingly, at the postsynaptic site, IGF-1 could inhibit the activity of glycogen synthase kinase 3 beta (GSK3β), a key factor in the hyperphosphorylation of the microtubule-associated protein (Tau). By reducing the activity of GSK3, IGF-1 could potentially prevent the formation of neurofibrillary agglomerates (an important pathological marker of AD disease). In addition, through phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) activation, IGF-1 may be involved in the incorporation and transport of glutamatergic receptors in dendrites [41].

## Conclusion

It is well known that age is the major risk factor for neurodegenerative diseases, and the endogenous level of neurotrophic factors decreases with age, suggesting that trophic factor loss may contribute to the etiology of neurodiseases. Neurodegenerative diseases such as Parkinson's disease or Alzheimer's disease and even the natural process of aging generate, as we detailed, several cognitive disorders and

motor dysfunctions associated with excessive ROS from cellular metabolism, alterations in growth factor production, in pro-inflammatory cytokines and inflammatory markers, and in neurotransmitter receptors expression, and structural changes in dendritic morphology and electrophysiological properties.

In this context, insulin-like growth factor-1 is an important neurotrophic factor/hormone with receptors widely expressed in the brain. It is affected in a range of neurodegenerative disorders and may play a role in brain dysfunction. It is well known that IGF-1 promotes neurogenesis and synaptogenesis in the postnatal dentate gyrus and acts as fast modulator of brain activity, specifically, in cognitive processes. Also, the chronic administration of IGF-1 or administration of Gly-Pro-Glu, an N-terminal peptide of IGF-1, attenuated loss of TH-immunoreactive cells, terminals, and behavioral deficits in response to 6-hydroxydopamine (6-OHDA) infusion into the dopaminergic axons within the nigrostriatal pathway. Moreover, IGF-1 therapy improved glucose and lipid metabolism, increasing testosterone levels and antioxidant ability and reducing oxidative damage, and it was also associated with a normalization of antioxidant enzyme activities.

Taken together, the IGF-1 action as neuroprotective molecule, the interaction with estrogen as neuromodulators, its crucial role in oxidative stress, and its important function in synaptic plasticity are valuable aspects to study and evaluate in depth of this growth factor considering that it may be a potential therapeutic molecule inside neurodegenerative diseases.

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