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Astrocytes Role in Parkinson: A Double-Edged Sword

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1. Introduction

Parkinson Disease (PD) is the second most chronic neurodegenerative disorder in the world, after Alzheimer's Disease (AD), and is estimated to affect about 1% of the population over 60 years of age. PD is caused by the disruption of dopaminergic neurotransmission in the basal ganglia, which causes a reduction in the numbers of dopaminergic neurons in the substantia nigra and formation of cytoplasmic inclusions called Lewy bodies [1].

Both in normal and pathological circumstances, astrocytes are critical supporters of neuronal function in processes such as antioxidant protection, glutamate clearance, the development and/or maintenance of blood brain barrier characteristics, the release of gliotransmitters and cytokines [2-4]. In recent years, much research on PD has focused on the astrocytic-neuronal crosstalk, suggesting that this interaction is important for future therapies against neurodegenerative processes. During brain damage events, astrocytes become transiently or permanently impaired, and the subsequent impact on neuronal cells may lead to pathological conditions such as PD [5-7].

In the present chapter, we provide a brief overview of the astrocytic functions and the pathophysiological events elicited during PD. Additionally, we explore the beneficial and damaging consequences of reactive astrogliosis in dopaminergic neurons during PD, particularly on oxidative damage, which is a main component of numerous neuropathological conditions, and that may have a damaging effect in astrocytic functions. We also highlight some of the cellular and animal models currently used in Parkinson research, such as rotenone, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and paraquat as inducers, which have many similar features with this disease. Finally, a brief overview of the future perspectives in astrocytic protection during Parkinson development is discussed.

2. Parkinson's disease

PD is a progressive neurodegenerative disorder caused by the neuronal death in the substantia nigra (SN), degeneration of dopaminergic neurotransmission, and the presence of α -synuclein and protein inclusions in neuronal cell bodies (Lewy bodies) [4-5,7]. Main symptoms of Parkinson are asymmetrical bradikinesia, rigidity, resting tremor and postural instability. Other non-motor symptoms that generate serious disability problems have also been noted, including fatigue, pain, Lewy Body dementia, psychosis, depression, and apathy [1]. Although there is not a cure for the disease, the most used and cheaper treatment for PD continues to be Levodopa [1,8]. However, about 40% of patients developed motor fluctuations and dyskinesias after 4 to 6 years of treatment [1], demonstrating that further pharmacological research is needed in order to counterbalance side effects. In this aspect, treatments using long-acting dopaminergic agents or a continuous dopaminergic effect in the striatum have been associated with less severe motor complications, given alone or in combination with L-dopa [9]. Some pharmacological agents that have shown promising applications, include dopamine agonist like apomorphine and ropinirole, and catechol-O-methyltransferase (COMT; EC 2.1.1.6) inhibitors [9].

Numerous reviews and articles agree that the exact cause of PD remains unknown [1,9-10]. Mutations in various proteins such as leucine-rich repeat kinase 2 (LRRK2; EC 2.7.11.1), Parkinson protein 2 (PARK2), probable cation-transporting ATPase type 13A2 (ATP13A2; EC 3.6.3.-), phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1; EC 2.7.11.1), and Parkinson disease (autosomal recessive, early onset) 7 protein (DJ-1) have been observed in familiar cases of Parkinson, which only accounts for 10-15% of diagnosed cases [6,11-12]. Interestingly, LRRK2, PINK1, and DJ-1, which are present in mitochondrial membranes, have been suggested to play a role in reactive oxygen species (ROS) production by a defective maintenance of the mitochondrial membrane potential [12-13].

A number of environmental factors have been found to induce PD-like symptoms, and are currently used in animal and cellular models of the disease. Environmental factors include vascular insults to the brain, oxidative stress, neuroleptic drugs and repeated head trauma. [6,14]. Additionally, the exposure to pesticides like rotenone or 1-methyl-4-phenylpyridinium (MPP⁺) and heavy metals (manganese) increases the risk of PD development [6, 10, 14-15]. In this aspect, numerous epidemiologic and toxicologic studies have examined pesticides as a risk factor for PD and parkinsonism and the possible mechanisms by which pesticides may act [14-17].

Initiation and progression of PD is dependent upon cellular events, including failures in the protein degradation machinery, oxidative stress, mitochondrial dysfunction, defects in mitochondrial autophagy (mitophagy) and the continuous accumulation of α -synuclein, driven through cell to cell interactions between glial cells and neurons that ultimately lead to apoptosis [7,10,18]. Previous studies pointed that astrocytic α -synuclein deposition initiates the recruitment of phagocyte microglia that attacks and kills neurons in restricted brain regions [7,19], correlating this α -synuclein accumulation with nigral neuronal cell death [20], and suggest the importance of astrocytes in the initiation of the disease. Conversely, astrocytes

also have beneficial roles during PD progression [21-22]. For example, astrocytes express different antioxidant molecules such as glutathione peroxidase (EC 1.11.1.9), which have been inversely correlated with the severity of dopaminergic cell loss in the respective cell groups in patients with PD [4].

3. Astrocytes in PD

3.1. Astrocytic functions

Astrocytes are the most common cell type in the mammalian brain, conforming the glia with oligodendrocytes and microglia [23]. They are characterized by the expression of the intermediate filaments glial fibrillary acidic protein (GFAP) and vimentin (Vim). Astrocytes are essential for the metabolism of the brain, transporting multiple nutrients and metabolic precursors to the neurons by the malate-aspartate shuttle and other transporters [24]. There are two main types of astrocytes in the SNC: Protoplasmic astrocytes, which envelope neuronal bodies and synapses and fibrous astrocytes which interact with the nodes of Ranvier and oligodendroglia [7]. Current research has shown that only protoplasmic astrocytes have an increase in the accumulation of α -synuclein, whereas fibrous astrocytes do not [7,19].

Current knowledge indicates that astrocytes are critical for some cellular processes, such as the development and/or maintenance of blood-brain barrier characteristics, the promotion of neurovascular coupling, the attraction of cells through the release of chemokines, K^+ buffering, release of gliotransmitters, release of glutamate by calcium signaling, maintenance of general metabolism, control of the brain pH, metabolization of dopamine and other substrates by monoamine oxidases (MAOs; EC 1.4.3.4), uptake of glutamate and γ -aminobutyric acid (GABA) by specific transporters and production of antioxidants [2-3,25-27] (Figure 1). Recent evidence has shown that astrocytes are arranged in non-overlapping domains forming a syncytial network that may contact approximately 160.000 synapses, thus integrating neural activity with the vascular network [4,28]. In this aspect, astrocytic terminal processes, known as endfeet, contact the brain vasculature and enwrap the neuronal synapses, enabling the modulation of both neuronal activity and cerebral blood flow, following an elevation in intracellular Ca^{2+} levels in the endfeet [24,29].

During brain damage (including diseases, brain injury and oxidative stress), these astrocytic functions become transiently or permanently impaired, and the subsequent impact on neuronal cells may lead to pathological conditions and neurodegenerative diseases [3,26]. Neurons are more susceptible to injury than astrocytes, as they have limited antioxidant capacity, and rely heavily on their metabolic coupling with astrocytes to combat oxidative stress [3]. However, severe brain damage also results in astrocyte dysfunction, leading to increased neuronal death [30].

As previously stated, astrocytes exert both neuroprotective and neurodegenerative roles, depending on the molecules released by them, and the pathological or normal circumstances of their microenvironment [6]. For example, astrocytes release antioxidant molecules like

glutathione (GSH) and superoxide dismutases (SODs; EC 1.15.1.1), and supply neurons with neurotrophic factors, such as nerve growth factor (NGF), basic fibroblast growth factor (bFG), that constitute an important attempt to protect neurons during brain damaging processes, including PD [6, 31-32]. On the other hand, during the process of reactive astrogliosis, astrocytes release inflammatory cytokines that may affect the surrounding neurons, both by the induced production of ROS and lipid peroxidation, and by the activation of apoptotic mechanisms that induce neuronal dopaminergic death [6,10]. These unusual, and sometimes contradictory, features of astrocytes in PD will be further explored in this chapter.

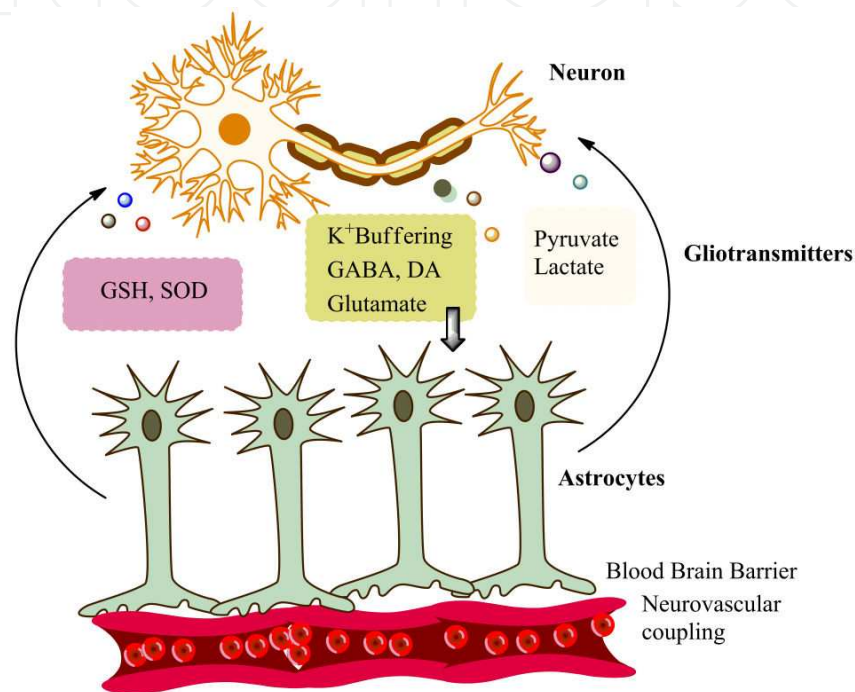


Figure 1. Astrocytes support neuronal function by multiple ways, including the development and maintenance of blood–brain barrier and promoting the neurovascular coupling. Astrocytes regulate the levels of ions, neurotransmitters and fueling molecules such as K^+ , glutamate, GABA, dopamine, lactate and piruvate. Furthermore, astrocytes promote the attraction of cells through the release of chemokines, and produce beneficial antioxidants, including glutathione, superoxide dismutases (SODs 1, 2 and 3), and ascorbate.

3.2. Astrogliosis and parkinson

Reactive astrogliosis is the main reaction of astrocytes following brain insults such as infection, trauma [33-34], α -synuclein accumulation [35], ischemia [36-37] and neurodegenerative diseases [3]. This process involves both molecular and morphological changes in the astrocytes, including increased expression of GFAP, vimentin and nestin, uptake of excitotoxic glutamate, protection from oxidative stress by the production of GSH, neuroprotection by release of adenosine, degradation of amyloid-beta peptides, facilitation of blood-brain barrier, increased formation of gap junctions between astrocytes, formation of scars and, in some cases release of inflammatory cytokines, including tumor necrosis factor- α (TNF- α), and production of ROS [3,35,38-40].

Astrogliosis and microgliosis in the SN of Parkinson patients are key features of the disease, which is a nonspecific consequence of neuronal degeneration [10]. Cellular and animal models using environmental and biological toxins, especially lipopolysaccharides (LPS), herbicides and pesticides like rotenone or MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), can induce both astrogliosis and microgliosis, which is accompanied by neuronal death, mitochondrial dysfunction and nuclear fragmentation [41-45]. Additionally, it was previously shown that the injection of LPS in rat brains was followed by an increase in the inducible nitric oxide synthase (iNOS; EC 1.14.13.39), suggesting that chronic glial activation can cause oxidative stress in the brain, similarly to that seen in neurodegenerative processes like AD and Parkinson [10, 39, 45]. A previous report showed that activated glial cells can participate in the death of dopaminergic neurons, probably by the activation of apoptosis by cytokines like TNF- α , IL-1 β , IL-6 and interferon- γ and the subsequent production of nitric oxide (NO) by the iNOS that may diffuse toward the neurons and induce lipid peroxidation, DNA strands breaks and inhibition of mitochondrial metabolism [6,10]. Furthermore, cytokines released by astrocytes may bind to their specific receptors in the dopaminergic neurons, such as TNFR1 and 2, and activate proapoptotic mechanisms through the activation of caspase 3, caspase 8, and cytochrome c [10]. Interestingly, the excessive uptake of neuronal α -synuclein by astrocytes can lead to accumulation of aggregates of this protein in astrocytes, and cause an upregulation of IL-1 α , IL-1 β and IL-6, followed by the release of TNF- α and IL-6 [6]. These results suggest that the inhibition of glial reaction to damage and further inflammatory processes could be considered as a promising therapy to reduce neuronal damage during PD [10].

3.3. Oxidative stress and Parkinson: Role of astrocytes

In the brain, oxidative stress and other toxic insults can trigger the overexpression and activation of neuronal nitric oxide synthase that increases NO production and may cause apoptotic cell death by inducing the release of cytochrome c from mitochondrial impairment, loss of membrane potential, the opening of permeability transition pores, and the release of proapoptotic molecules [46,47]. After brain damaging processes, neurons experience greater metabolic deterioration than glial cells. For instance, astrocytes contain glycogen stores that allow them to maintain ATP production through glycolysis and mitochondrial membrane potential by reversal of the F₀-F₁-ATPase (EC 3.6.3.14) [48]. For example, cultured astrocytes subjected to oxygen and glucose deprivation showed a decrease in mitochondrial membrane potential, possibly caused by the mitochondrial permeability transition pore (mtPTP) opening, which leads to a loss of intramitochondrial contents, mitochondrial respiration and ATP production [48].

Nowadays there is much evidence of the role of oxidative stress in the development of neurodegenerative diseases, such as AD, PD, Amyotrophic Lateral Sclerosis (ALS) and Huntington's disease (HD). Much of these oxidative damaging processes are associated with an imbalance on the production of ROS that leads to mitochondrial stress and impairment in energy production [47,49]. ROS, such as superoxide (O $\cdot$ 2 $\cdot$), can be produced

in mitochondrial complexes I and III in components of the tricarboxylic-acid cycle, including α -ketoglutarate dehydrogenase (EC 1.2.4.2), and in the outer mitochondrial membrane, damaging cell components such as lipids, proteins and DNA [25, 47]. In PD, oxidative damage is a common feature, as demonstrated by increased levels of ROS in post-mortem PD brain samples [25]. Oxidative stress seems to affect various brain regions, including the SN and caudate nucleus, and it is accompanied by an increase in GFAP and astrocytic proliferation [50]. Additionally, PD patients present deficiencies in mitochondrial complex I in the SN, suggesting that a defect in this complex could contribute to neuronal degeneration in PD [25]. However, it is not clear whether the damage induced by ROS is a cause or a consequence of other cellular dysfunctions [25]. For example, a previous study on PD brains showed an increase in lipid peroxidation products, such as 4-hydroxynonenal, and in protein crosslinking and fragmentation [51], suggesting that oxidative stress may affect other brain regions apart from the SN.

Astrocytes produce numerous antioxidant molecules, such as GSH, catalase (EC 1.11.1.6) and SODs, providing further antioxidant protection to neurons. Unfortunately, it is known that the astrocytic protection afforded to neurons is limited, possibly due to a decline in GSH trafficking by chronic iNOS induction [52]. This depletion of GSH may facilitate the production of ROS and reactive nitrogen species (RNS) by astrocytes, causing alterations in neuronal proteins such as α -synuclein [25]. Furthermore, the nitration of α -synuclein by RNS can significantly enhance the synuclein fibril formation *in vitro*, similarly to what happens in PD brains [25]. In sum, the antioxidant properties of astrocytes have a fundamental role in the development of neurodegenerative diseases, and are considered as promising therapeutically targets.

4. Experimental models in Parkinson

Various pesticides, herbicides and drugs have been used in animal and *in vitro* models of Parkinson, as their effects mimic similar features of that seen in PD. Different epidemiological studies have shown a correlation between the exposure of these substances (especially in the case of pesticides) and appearance of PD [14-15, 17, 53]. A common feature of many of these neurotoxic compounds, such as rotenone, paraquat, or MPTP, is the inhibition of mitochondrial complex I, followed by the overproduction of ROS, ATP exhaustion, and induction of a wide range of abnormalities that can elicit neuronal and astrocytic cell death [54]. Additionally, neurotoxins induce nuclear fragmentation, endoplasmic reticulum (ER) stress and unfolded protein response in catecholaminergic cells, which are associated with changes in proteasomal and chaperone activities, similar to those observed in PD [45,55]. Other molecules used in PD models include the fungicide maneb, cyclodienes, organophosphates such as deltamethrin, DDT (dichlorodiphenyltrichloroethane), 2,4-dichlorophenoxyacetic acid, dieldrin, deguelin, diethyldithiocarbamate, paraquat, maneb, trifluralin and parathion (Figure 2) [15,56].

Experimental Models in Parkinson Disease

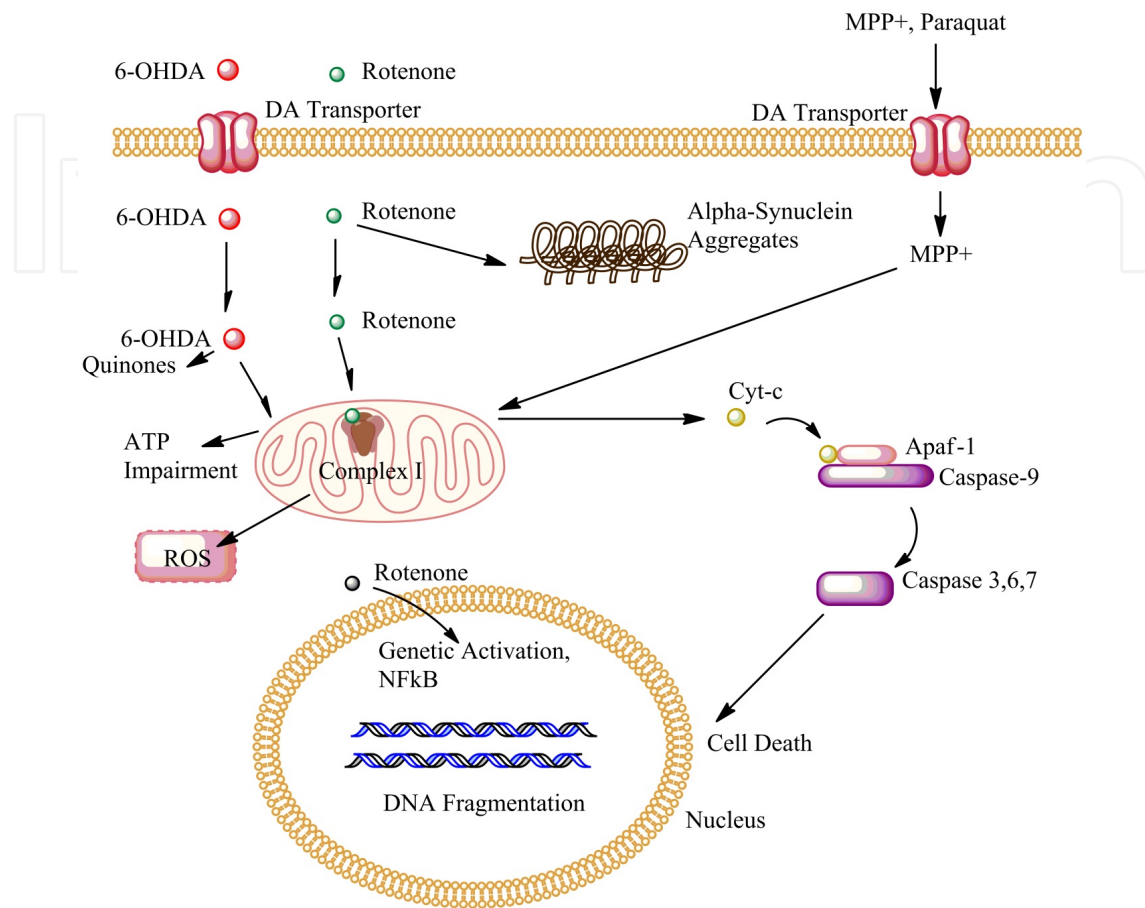


Figure 2. Experimental models in PD. Many molecules are currently used in cellular and animal models of PD, including pesticides as paraquat or rotenone and neurotoxins such as 6-OHDA and MPP⁺. Paraquat, 6-hydroxydopamine (6-OHDA) and MPP⁺ easily cross cell membrane through the dopamine transporter (DA) thus inducing the formation of α -synuclein aggregates and mitochondrial impairment with the subsequent production of ROS and quinones. Compounds, as rotenone, are extremely hydrophobic and penetrate easily the cellular membrane of neurons and astrocytes. Rotenone may promote processes such as the formation of α -synuclein aggregates, and the genetic activation through the nuclear translocation of NF- κ B. Additionally, as an inhibitor of mitochondrial complex I, rotenone causes the impairment of ATP, the generation of ROS and the release of proapoptotic molecules, such as cytochrome c that activate caspase 9, which trigger caspases 3, 6 and 7, and induce apoptosis.

4.1. Rotenone as a Parkinson model

Rotenone is one of the most studied neurotoxic substances used as a model for PD features and oxidative stress events in cellular and animal models [14,57]. Rotenone is a naturally occurring isoflavonoid produced in the leaves, roots and rhizomes of the tropical legumes from the genres *Derris*, *Lonchocarpus*, and *Tephrosia*. It is extremely hydrophobic and crosses biological membranes and serves as a high-affinity noncompetitive inhibitor of complex I, thus affecting ATP generation [58]. Rotenone is commonly used in solution as a pesticide, insecticide, or in emulsified liquid form as a piscicide [59,60].

Rotenone, and other complex I inhibitors, such as MPTP, paraquat and maneb, are used as models for assessing the environmental causes of PD [12]. Previous epidemiological studies have supported the hypothesis that a prolonged exposure to pesticides is a risk factor for PD [17, 57, 61]. Furthermore, a recent case-control study from the NIH, which reviewed 110 PD cases and 358 controls, and observed that PD incidence was increased 2.5 times in individuals who reported use of rotenone compared with nonusers [17]. Another study in agricultural workers from East Texas identified a significant increased risk (OR = 10.9) of PD with the continuous use of rotenone [53]. Although these reports raised important concerns on the use of rotenone, further studies are needed to assess the detailed global epidemiology of PD by this pesticide.

Much of the research on rotenone has used animal models and different routes of administration for evaluating its effects in the Central Nervous System (CNS), especially in neurons [14, 57]. Several groups have demonstrated that continuous systemic administration of rotenone to rats and mice reproduces key features of PD, including selective degeneration of the nigrostriatal dopaminergic system, activation of astroglia and microglia, formation of cytoplasmic inclusions in neurons, movement disorders, and defects in mitochondrial complex I [11, 14, 57, 62-64]. Previous studies have shown that intracerebral administration of rotenone damages the nigrostriatal dopaminergic pathway in rats, including the striatum fibers and neurons [14, 57]. However, the doses employed in those experiments were much higher than the standard IC_{50} for rotenone. For example, doses of 2-3 mg/kg/day, similar to that reported in platelets from PD patients, produced complex I inhibition with selective nigrostriatal degeneration and astrocyte activation [14, 65]. In this matter, neuronal death is thought to be a consequence of the inhibition of mitochondrial complex I, which leads to a reduction in the energy supply and subsequent collapse of the mitochondrial membrane potential [66]. A recent study suggests that rotenone administration activates caspase-2 in mice neurons inducing the activation of downstream apoptotic effectors such as Bid, Bax, caspase 3 and 9, thus initiating apoptosis [67]. Similarly, the exposure of human dopaminergic SH-SY5Y cells to rotenone caused the nuclear translocation of nuclear factor κB (NF- κB) and the activation of caspase-3, suggesting that complex I deficiency induced by rotenone can induce NF- κB -mediated apoptosis (Figure 3) [68].

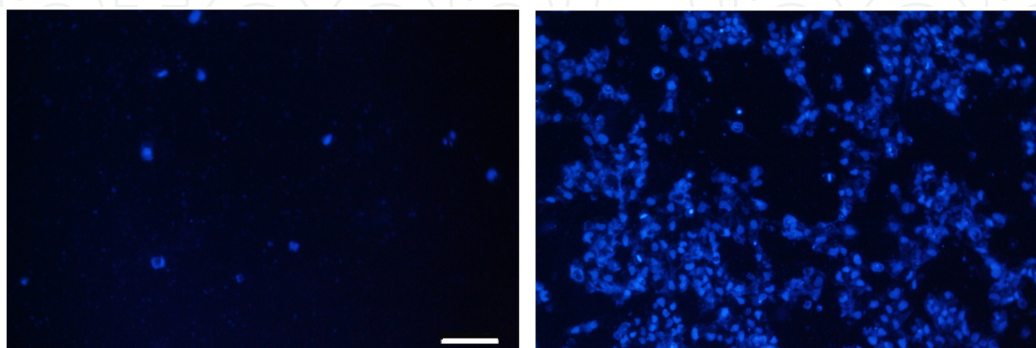


Figure 3. Rotenone-induced cell death. Astrocytic cell line ESP12 cells were treated with 30 nM of rotenone (right) or control (left), and stained for Hoechst 33258 to assess nuclear fragmentation. Rotenone-treated cells showed increased nuclear damage compared to controls. Scale bar, 50 μm .

Alternatively, it has been postulated that rotenone-induced dopaminergic neuronal death could be dependent on the inflammatory process associated with microglial activation [64] thus indicating that rotenone differentially affects various types of CNS cells. Other previous experiments have shown that subcutaneous administration of rotenone resulted in a highly selective dopaminergic damage in neurons and α -synuclein aggregation, similar to the Lewy bodies of PD [63,65]. The mechanisms by which rotenone upregulates α -synuclein and causes its aggregation, are not well understood. A possible hypothesis is that aggregation is probably a consequence of oxidative modifications of α -synuclein [69]. For instance, neurons and astrocytes treated with rotenone (25 to 50 nM) showed an altered expression of g-tubulin and a disorganization of the centrosome with aggregates of α -synuclein [70]. Similarly, other studies suggest that inhibition of mitochondrial complex I activity and facilitation of α -synuclein aggregation may be closely associated with rotenone's selective dopaminergic toxicity in neurons [14,65]. Furthermore, a different approach using intragastrically administered rotenone (5 mg/Kg) in mice showed that the accumulation and aggregation of α -synuclein in neurons of the dorsal motor nucleus of the vagus (DMV) and the intermediolateral nucleus (IML) in the spinal cord was accompanied by the selective loss of dopaminergic neurons and astrogliosis, suggesting that the gastric administration of rotenone through the connection of the enteric nervous system (ENS) with anatomical structures of the CNS also induces PD-like features [11,19]. Rotenone has also been shown to cause increased expression of connexin43 (Cx43), which forms gap junctions, and P2X7 receptors that modulate cytokine secretion and gamma tubulin; these are important for the adequate function of the cytoskeleton and organelles such as the Golgi apparatus [70-73]. Moreover, rotenone induces astrogliosis and alterations in the expression of g-tubulin, signal transducer and activator of transcription 3 (STAT3), and connexin 43 in astrocytes [70, 72, 74].

In sum, the *in vitro* and *in vivo* evidences presented here show that dopaminergic neurons are more sensitive to rotenone toxicity than non-dopaminergic neurons, amacrine cells of retina and astrocytes [55, 75-77], possibly due to their lesser effective oxidative mechanisms and reduced supply of antioxidants [30,78]. However, astrocytes are more resilient to rotenone treatment than neurons, being its mitochondrial dysfunction tightly associated with increased neuronal death [2-4,74].

4.2. MPTP and Parkinson

MPTP is a widely used neurotoxicant, known for the induction of Parkinson-like symptoms such as bradikinesia, movement disorders, α -synuclein bodies, mitochondrial abnormalities, sustained inflammation in the substantia nigra and activation of the microglia [6,10,15, 79-80]. It was initially shown that in drug addicts, who were accidentally exposed to MPTP, there was a depletion of pigmented nerve cells in the substantia nigra, accompanied by astrogliosis and clustering of microglia around nerve cells [41], thus presenting some PD-like features.

MPTP is an alipophilic prototoxin that rapidly crosses the blood-brain barrier and damage dopaminergic neurons due to the selective uptake of the active metabolite MPP⁺ via the dopamine transporter [80]. Similarly to rotenone, its neurotoxicity is induced by the inhibition of mitochondrial complex I, and subsequent energy depletion [80-81]. Additionally, MPP⁺ has

high affinity for noradrenergic and serotonergic uptake transporters [6,82], and its precursor, MPTP, has been mainly used in neuronal models with dopaminergic characteristics, such as the dopaminergic neuroblastoma cell line SH-SY5Y [83]. In astrocytes, MPTP has shown different (and sometimes contradictory) effects according to the experimental evidence collected in cellular and animal models. For instance, Rappold and Tieu (2010) showed that MPTP is metabolized by the astrocytic monoamineoxidase-B (MAO-B) and converted to the toxic cation MPP⁺, which is extruded to the extracellular space through the organic cation transporter 3 (oct3) [6, 84]. Afterwards, MPP⁺ is taken by neighboring dopaminergic neurons, thus inducing neuronal death [84]. Interestingly, silencing of oct 3 transporter in mice attenuates both the MPP⁺ release from astrocytes and the subsequent impairment of dopaminergic neurons, in which makes oct3 as an important molecular target for dopaminergic related pathologies [6,84]. On the other hand, other authors have shown that MPP⁺ induces negative effects in astrocytes, such as loss of viability, impairment of energetic metabolism of mitochondria, ROS generation and decrease in the glutamate clearance by astrocytes [81,85,86]. Taking into account the importance of MPTP, as a model for PD, it seems that further epidemiological research is needed to address more thoroughly the role of MPTP in astrocytic damage and PD development.

4.3. Other toxic compounds involved in Parkinson development: Paraquat and 6-OHDA

The pesticide *N,N'*-dimethyl-4,4'-bipyridinium dichloride (paraquat), which shares similar structure with MPP⁺, impairs mitochondrial functions by inducing an augmented production of oxidative stress and 4-hydroxynenal *in vivo* [87]. Although paraquat may not be an efficient inhibitor of mitochondrial complex I, and so does not affect dopamine uptake [87,88], it does cause α -synuclein aggregation in C57Bl/6 mice, and alters Parkin solubility, decreasing proteasome activity and causing cellular damage [87].

Paraquat has been previously shown to induce PD-like neuronal dopaminergic lesions in animal models and neuronal cell lines (Brown et al., 2006; Berry et al., 2010). Additionally, epidemiological studies suggest that long-term exposure to paraquat is associated with PD development [15,89]. To counteract this oxidative damage induced by paraquat, and MPTP, astrocytes seem to protect dopaminergic neurons by increasing expression of antioxidant molecules, such as heme oxygenase1 (EC 1.14.99.3), glutathione S-transferase P (EC 2.5.1.18) and glutathione [90,91]. Although this protective role of astrocytes on neuronal death by paraquat is quite promising, only few studies address this interaction and further research is needed in order to establish the precise effect of paraquat in astrocytes metabolism and neuroprotection.

Similarly to paraquat, 6-Hydroxydopamine (6-OHDA) is another widely used for *in vivo* and *in vitro* animal models of PD [92]. This compound has a structure similar to dopamine and norepinephrine and exhibits a high affinity for catecholaminergic transporters such as dopamine DAT (Dopamine transporter). 6-OHDA induces dopaminergic neuronal death by the increased generation of H₂O₂ and quinones [92]. Additionally, it causes both microgliosis and astrogliosis, which is characterized by increased astrocytic proliferation in rat cortex and striatum accompanied by a marked expression of GFAP [92,93]. Taking into account that reactive astrocytes may produce various neurotrophic factors and antioxidant mole-

cules targeting neuronal survival, it is possible that genetic manipulation of these functions in astrocytes may represent a promising strategy to improve dopaminergic neurons or neural progenitor cells survival [4,23]. These neuroprotective features of astrocyte in Parkinson are further explored in the following topic.

5. Astrocytic neuroprotection in Parkinson

Over the last years, much research has focused on specific molecules produced by astrocytes that exert neuroprotection during brain injuries and diseases including PD, both through the reuptake of glutamate, or by producing gliotransmitters, antioxidant enzymes such as SODs, growth factors, peptide hormones and heat shock proteins [4,94-98]. Many of them have shown protective effects both in dopaminergic neurons and glial cells, and have been used in animal models and clinical trials with remarkable results (Figure 4) [31,32].

5.1. Glutathione and Parkinson

Astrocytes produce beneficial antioxidants, including glutathione, superoxide dismutases (SODs 1, 2 and 3), and ascorbate, which are important for neuronal survival during neurodegenerative processes [95,99-101].

The tripeptid glutathione, as the main antioxidant in the brain, is needed for the conversion of methylglyoxal, a toxic by-product of metabolism, into d-lactate by glyoxalase 1 (EC 4.4.1.5) [94,95]. GSH is also important in limiting and repairing the deleterious actions of NO, but unfortunately GSH levels can be depleted by extremely high concentrations of NO [23]. For example, glutathione becomes rapidly oxidized to glutathione disulfide either by glutathione peroxidase (GPx) or by enzyme-independent chemical reactions [102]. This is an important effect against ROS formation in PD, as it helps reducing the inhibition of complex I by NO [103]. Astrocytes possess a greater concentration of glutathione (3,8 mmol/L) than neurons (2.5 mmol), probably due to a higher content of the astrocytic enzyme γ -glutamyl-cysteine synthetase (EC 6.3.2.2) [6]. For example, neurons co-cultured with astrocytes exhibit higher levels of glutathione compared to neurons cultured alone, demonstrating that astrocytes provide additional antioxidant defenses to neurons [104-106]. Additionally, an increase in glutathione peroxidase-containing cells shows to be inversely correlated with the severity of dopaminergic cell loss in cell populations from patients with PD, suggesting that the quantity of glutathione peroxidase in cells might be critical for a protective effect against oxidative stress during PD [107].

The greater production of GSH by astrocytes seems to be dependent on the preferential activation of transcription factor Nrf2 in astrocytes, which leads to a more efficient GSH synthesis and higher GSH content in astrocytes than in neurons [108]. Interestingly, Nrf2 is known to regulate the expression of cytoprotective genes, and factors essential to neuronal survival [6,108]. Additionally, Nrf2 knockout mice are more sensitive to mitochondrial complex inhibitors such as MPTP and 3-nitropropionic acid [108], suggesting an important role of this transcription factor in scavenging free radicals. On the other hand, decrease in glutathione is

one of the earliest biochemical changes in PD and incidental Lewy body disease [109]. Additionally, the GSH content was significantly reduced in the substantia nigra of PD patients, suggesting that GSH depletion enhances neuronal death under certain pathological conditions [6]. Interestingly, this evidence is consistent with the data in PD patients, in which glutathione-containing cells are in regions with preserved dopaminergic neurons [52].

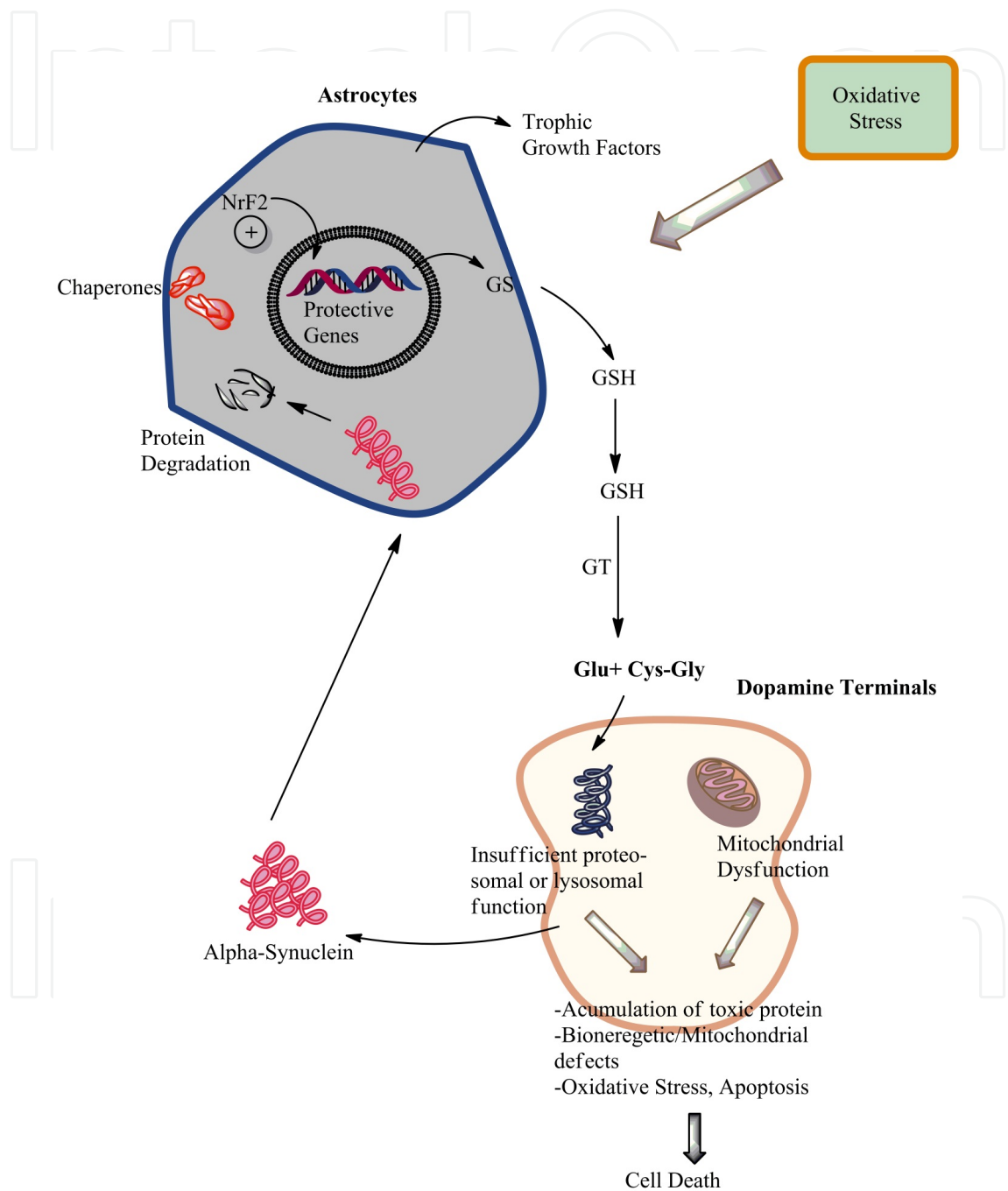


Figure 4. Astrocytes-mediate neuroprotection through multiple signaling pathways Astrocytes release glutathione, which serves as precursors for neuronal GSH synthesis, and trophic growth factors such as bFGF, GDNF, and MANF. Activation of the transcription factor Nrf2 leads to the expression of antioxidant genes, including γ -glutamylcysteine synthetase (GS), which is involved in GSH synthesis and removal or degradation of cytotoxic molecules, such as α -synuclein.

It is possible that the recovery of glutathione levels may enhance the survival of affected neurons, either by increasing synthesis of GSH or by slowing its degradation [25]. However, the GSH blood-brain barrier permeability is low, and clinical trials using injections of GSH have shown little benefits [6,25,110]. Alternatively, it has been demonstrated that the use of GSH precursors, such as glutamyl cysteine ethyl ester (GCEE) and glutathione ethyl ester (GEE), increases significantly the intracellular glutathione levels in neuronal cells, protecting dopaminergic neurons against oxidative and nitrosative stress, both in animal and cellular models [25,109]. Finally, the modulation of Nrf2 downstream signaling may be considered as a promising strategy for enhancing the astrocytic production of GSH [108], which may counteract the oxidative imbalance that likely affects neurons in neurodegenerative processes such as PD.

5.2. Superoxide dismutases and Parkinson

Superoxide dismutases catalyze the dismutation of superoxide ions into oxygen and hydrogen peroxide [23]. As such, they are an important antioxidant defense in nearly all cells exposed to oxygen. In most mammalian cells, SOD is present in three isoforms: a cytosolic copper, zinc superoxide dismutase (SOD1); a mitochondrial manganese superoxide dismutase (SOD2); and an extracellular copper, zinc superoxide dismutase (SOD3) [23, 112]. Given its importance in neuroprotection, SODs and other antioxidant molecules released by astrocytes are highly studied in neurodegenerative diseases like PD and in other oxidative-related events. Evidence that SODs defend against oxidative stress *in situ* has been obtained using transgenic mutants that either overexpress or lack these antioxidant enzymes [111]. For example, the overexpression of Cu/Zn SOD was able to rescue dopaminergic neurons and diminishes locomotor disabilities in a *Drosophila* mutant model for α -synuclein overexpression [112]. Interestingly in PD patients, it has been shown, an specific increase in SOD levels in the substantia nigra, with no changes in activities of glutathione peroxidase, catalase and glutathione reductase (EC 1.8.1.7) [25]. A similar increase was observed in the mitochondrial isoform of SOD in the motor cortex from PD patients [113], suggesting that SODs have a greater importance than other antioxidant enzymes during PD development. Further research is needed in order to address the therapeutic application of SOD in PD and other diseases.

5.3. Astrocytic chaperones and Parkinson

Chaperones belonging to the conserved family of Heat shock proteins (Hsps) are proteins involved in the regulation of protein folding, translocation of proteins across membranes, regulation of cell death and assembling of protein [114]. Interestingly, protein aggregates, and misfolded proteins have been found in AD, Huntington, PD, prion disease, ALS and other neurological injuries [115-117]. Furthermore, previous evidence suggests that formation of unfolded proteins in astrocytes could induce the inflammatory responses previously mentioned [117].

Many Hsps are currently being considered for the potential treatment of diseases involving protein aggregation and misfolding such as the case of PD [116,118]. These include the chap-

erones, DJ-1, Hsp70, Hsp9- and the co-chaperone Hsp40, and members from the Bag family, such as Bag 5, CHIP and suppression of tumorigenicity 13 (ST13) [118]. Several of these chaperones are colocalized or associated with the PD related proteins, E3-ubiquitin ligase (E 6.3.2.19), parkin, α -synuclein and the dopamine transporter (DAT) [119].

DJ-1, also known as PARK7, is upregulated in reactive astrocytes and serves as a redox-sensitive chaperone with antiapoptotic properties [119]. DJ-1, both in normal and mutant forms, colocalizes with Hsp70 and CHIP in the cytosol. Following oxidative stress, this molecule is translocated to the mitochondria, where it becomes associated with the chaperone GRP75 [119,120]. It has been previously shown that DJ-1 can suppress the aggregation and oligomerization of α -synuclein, thus promoting its degradation, which is dependent on the redox state of the cell environment [119,121]. Additionally, DJ-1 regulates signaling pathways such as P38 mitogen-activated protein kinases (MAPK; EC 2.7.11.24), apoptosis signal-regulating kinase 1 (ASK1; EC 2.7.11.25) and protein kinase B (AKT) following cellular production of ROS, suggesting that this chaperone is an important redox-reactive molecule during oxidative stress in PD and other age-related disorders [120].

Hsp70 family of chaperones are thought to be critical in the regulation of protein oligomerization and aggregation, which are believed to be central in the molecular pathogenesis of PD and other neurodegenerative diseases [118]. For example, the overexpression of Hsp70 has been found to protect PC12 cells, and dopaminergic neurons against MPTP toxicity [118,119]. Additionally, the overexpression of Hsp70 in mice has been shown to reduce the amount of misfolded and aggregated α -synuclein species, suggesting a protection of this chaperone against α -synuclein-dependent toxicity [122]. It seems that α -synuclein degradation mediated by Hsp70 occurs in the proteasome or in the lysosomes by a selective process called chaperone-mediated autophagy (CMA) [114]. The wild type, but not a mutant form of α -synuclein is degraded by CMA, suggesting that this mechanism is important in the formation of α -synuclein aggregates during PD [114]. Importantly, the astrocytic clearance of α -synuclein by chaperones, like Hsp70, may confer additional neuroprotection to dopaminergic neurons [6,114].

Chaperones located in other organelles, such as the ER, have also been studied in the development of neurodegenerative processes. For example, homocysteine-induced endoplasmic reticulum protein, which is located in the ER membrane of neurons and astrocytes in the Central Nervous System (SNC), is found accumulated in Lewy bodies, suggesting a role in their formation and further development of PD [117]. In sum, given the central importance of chaperones in protein homeostasis, or proteostasis, they may serve as rational targets for the design of therapeutic strategies in neurodegenerative diseases associated with aberrant protein folding including PD.

5.4. Growth factors and Parkinson

Several neurotrophic and growth factors have been shown to protect dopaminergic neurons and glial cells against induced excitotoxicity by the activation of specific signaling pathways that are responsible for cell survival and axonal sprouting [31,32]. Some of them have also been tested in PD clinical trials with some promising results [31,32]. For example, brain derived neurotrophic factor (BDNF) and TNF protect neurons against excitotoxicity through

activation of the transcription factor NF- κ B, which induces the expression of antioxidant enzymes such as Mn-SOD and the anti-apoptotic proteins, Bcl-2 and inhibitor of apoptosis proteins IAPs [123,124]. Additionally, the endogenous administration of BDNF was shown to protect neurons within the substantia nigra from 6-OHDA and MPTP toxicity, both in rat and primate Parkinson models [31].

The family of glial cell line-derived neurotrophic factor (GDNF) comprises ligands such as GDNF, neurturin (NRTN), artemin (ARTN) and persephin. GDNF, secreted by astrocytes, is essential for the survival of dopaminergic neurons [32]. It has been shown that GDNF administration by catheter increases dopaminergic neuronal resistance against 6-OHDA toxicity, but with preservation of motor functions in rat and rhesus monkey models [96]. However, clinical trials in patients that were administered GDNF in different regions of the brain have shown mixed results and further research is needed [31, 125-127].

Insulin-like growth factors (IGFs) signaling through the phosphatidylinositol 3-kinase (PI3K/Akt) downstream pathway can protect neurons against LPS excitotoxicity in cell culture and *in vivo* [124, 128,129]. Furthermore, the activation of this signaling pathway by IGF-I can suppress α -synuclein aggregation and toxicity, suggesting a possible therapeutically strategy in PD [130]. Similarly to IGF-I, vascular endothelial growth factor (VEGF) affects the survival and proliferation of endothelial cells, neurons and astrocytes in the brain, suggesting a potential therapeutic application in PD [32]. Additionally, VEGF-B (isof orm B) was found activated in a rat brain model following treatment with 40 nM rotenone, and showed neuroprotective actions by improving neuronal survival (Falk et al., 2009). Some studies suggest that VEGF promotes neuroprotection by signaling through the neuropilin receptor expressed in DA neurons, and indirectly by activating the proliferation of astroglia and by promoting angiogenesis [32,131,132]. Furthermore, the striatal injection of an adeno-associated virus (AAV)-mediated VEGF expression provided neuroprotection and behavioral improvement in rats treated with 6-OHDA [133].

Basic fibroblast growth factor (bFGF) protects hippocampal and cortical neurons against glutamate toxicity by changing the expression of N-methyl-D-aspartic acid (NMDA) receptors and antioxidant enzymes like superoxide dismutases and glutathione reductase [124]. Furthermore, a coculture of transgenic overexpressing FGF-2 Schwann cells with dopaminergic neurons improved the survival of dopaminergic neurons and the behavioral outcome in a parkinsonian rat model lesioned with 6-OHDA [134]. Finally, there are other neurotrophic factors that have shown dopaminergical neuronal protection in Parkinson-like models, including hepatocyte growth factor (HGF), mesencephalic astrocyte-derived neurotrophic factor (MANF), cerebral dopaminergic neurotrophic factor (CDNF), granulocyte colony-stimulating factor (G-CSF), and platelet derived growth factor (PDGF-CC) [31-32, 135-136].

6. Conclusions and future perspectives

In recent years a growing body of evidence has demonstrated that the malfunctioning of astrocytes may contribute to various neurodegenerative diseases, including Alzheimer, ALS,

multiple sclerosis, and Parkinson. Importantly, astrocytes are involved in both exacerbation of damage and in neuroprotective mechanisms that are crucial for neuronal survival. In this matter, astrocytes are essential for the regulation of oxidative stress and ROS production, both in normal and in pathological circumstances.

The overexpression of antioxidant molecules such as GSH and SOD2, or chaperones such as Hsp70 has proved to be a successful experimental approach in brain diseases, including PD. The use of growth factors, both in animal models and in clinical trials, has shown promising effects in protecting dopaminergic neurons and astrocytes in damaged regions by the activation of different signaling pathways important in neuronal survival and regeneration. It is important to mention that mitochondrial protection in astrocytes is an important asset to maintain the energetic balance of the brain and the antioxidant production that contribute to neuronal protection. Therefore future efforts in neuroprotective strategies should emphasize the mitochondrial protection in astrocytes. Finally, the combination of novel drug therapies, a better understanding of the α -synuclein clearance by astrocytes, the use of neurotoxic models, growth factors use and other therapies that increase astrocyte survival and its antioxidant function may shed light on a prospective cure of PD in the near future.

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