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Growth Factors and Neuroglobin in Astrocyte Protection Against Neurodegeneration and Oxidative Stress

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Abstract

Neurodegenerative diseases, such as Parkinson and Alzheimer, are among the main public health issues in the world due to their effects on life quality and high mortality rates. Although neuronal death is the main cause of disruption in the central nervous system (CNS) elicited by these pathologies, other cells such as astrocytes are also affected. There is no treatment for preventing the cellular death during neurodegenerative processes, and current drug therapy is focused on decreasing the associated motor symptoms. For these reasons, it has been necessary to seek new therapeutical procedures, including the use of growth factors to reduce α-synuclein toxicity and misfolding in order to recover neuronal cells and astrocytes. Additionally, it has been shown that some growth factors are able to reduce the overproduction of reactive oxygen species (ROS), which are associated with neuronal death through activation of antioxidative enzymes such as catalase, superoxide dismutase, glutathione peroxidase, and neuroglobin. In the present review, we discuss the use of growth factors such as PDGF-BB, VEGF, BDNF, and the antioxidative enzyme neuroglobin in the protection of astrocytes and neurons during the development of neurodegenerative diseases.

Keywords PDGF-BB · Neuroglobin · Astrocyte · Oxidative stress · Neurodegeneration

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Introduction

Neurodegenerative diseases are among the main public health problems in the world. It has been estimated that by the year 2020, there will be around 40 million people affected in the world by pathologies such as Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy, multiple sclerosis, and cerebrovascular accidents. Likewise, it is expected that by 2030, mortality from neurodegenerative diseases will reach 12.22% of global population [1].

PD manifests with a heterogeneity of symptoms such as resting tremor, bradykinesia, muscle hypertonia, postural instability, and cognitive and language alterations, which seriously affect the quality of life in patients [2, 3]. These symptoms are due to the selective degeneration of dopaminergic neurons (DA) of the substantia nigra pars compacta (Fig. 1), which results in an exacerbated decrease in dopamine levels [4–6].

The current pharmacological treatments for PD such as levodopa, carbidopa, dopamine receptor agonists, COMT (catechol-O-methyltransferase), or MAO-B (monoamine oxidase) inhibitors and deep brain stimulation are symptomatic and mainly focus on maintaining or prolonging the daily

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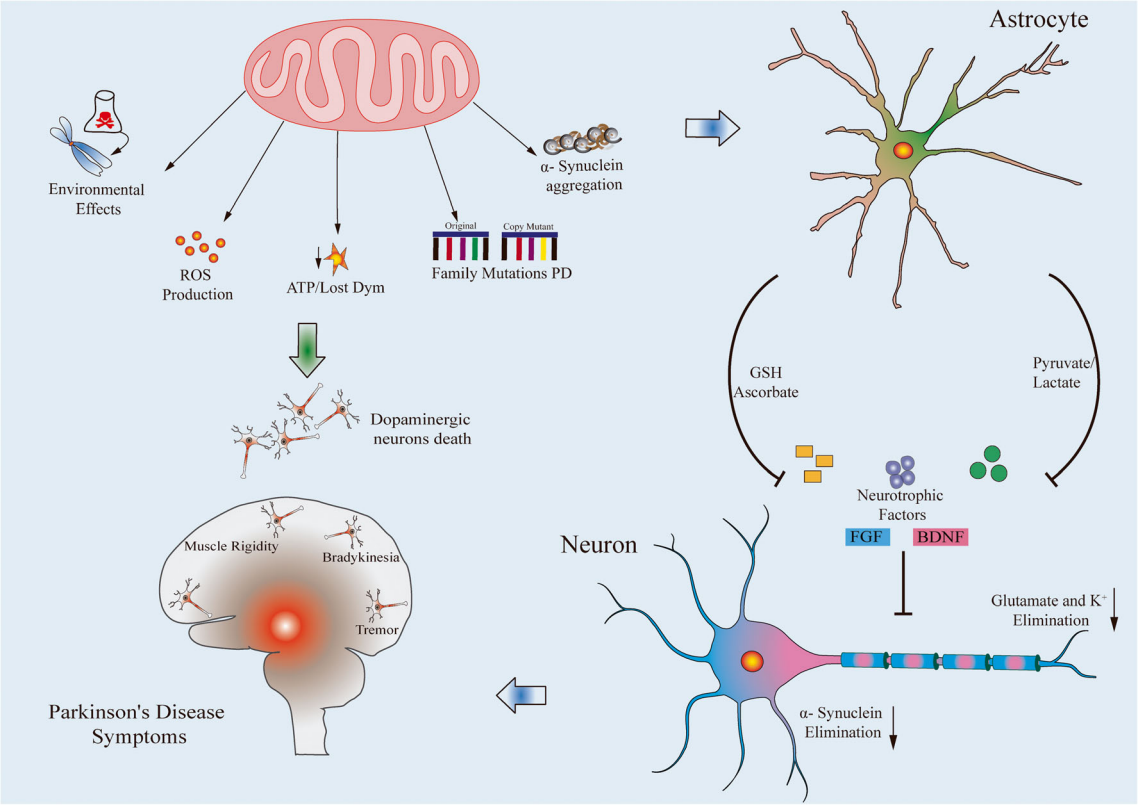

Fig. 1 Mitochondrial effects in PD. Alterations in mitochondrial proteins (parkin (PARK2) or PINK1) due to mutations or environmental effects may induce mitochondrial damage and increase ROS, along with drop in membrane potential mitochondrial ($\Delta\Psi m$), formation of α-synuclein aggregates, and activation of apoptotic mechanisms in DAs are considered as hallmarks during PD onset

activities of patients, without interfering with the progression of the disease [7–9]. Likewise, these pharmacological treatments lead to motor complications in 50–90% of cases together with a loss in their effectiveness after 2 to 5 years [8]. For this reason, it has been necessary to seek new treatments and methodologies for this pathology including the use of simvastatin and other non-steroidal agents, overexpression of chaperone proteins such as GRP78 to reduce misfolding and α-synuclein toxicity, transplantation of mesenchymal stem cells, spinal cord electric stimulation, and the use of growth factors [10–13].

Different growth factors such as fibroblast growth factor (FGF), brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), nerve growth factor (NGF), and platelet-derived growth factor (PDGF) have been used in various models of neuroprotection including cell lines, animal models, and clinical trials. It has been observed that these growth factors protect neurons and glial cells against excitotoxic and oxidative insults through the production of antioxidant enzymes, chaperones, activation of cellular survival pathways, and mitochondrial protection [13–18]. Unfortunately, growth factors such as BDNF and NGF, when used in human clinical trials, showed harmful side effects including nausea and extreme pain [19].

In the case of PDGF, it has been shown that some isoforms have neuroprotective effects against ischemic damage in rat pyramidal neurons, N-methyl-D-aspartate (NMDA) insult in retina of murine models, 6-OHDA in neurons, and TAT toxin of HIV [18, 20–22]. Similarly, recent clinical trials have reported that intracerebroventricular infusion of different doses of platelet-derived growth factor, isotype BB (PDGF-BB) produced no adverse effects in patients [13]. These results suggest that PDGF-BB has promising protective effects in the treatment of neurodegenerative diseases including PD.

Although dopaminergic neurons are the main cells affected in PD, numerous studies have demonstrated the participation of glial cells (microglia, astrocytes, and oligodendroglia) in the development of inflammatory events and degenerative processes that are present in PD [23–26]. These include augmented astrocytic reactivity in post-mortem brains of patients with PD, increased release of interferon-γ and neurotrophic factors, high levels of glutathione peroxidase (GPx), and increases in the endocytosis of α-synuclein by astrocytes [27]. Taking into account the abovementioned findings, this review highlights the need for novel neuronal and astrocytic protection strategies. We also sought to provide evidence on the efficacy of new protective molecules such as neuroglobin (ngb1), PDGF-BB, and other growth factors and to introduce

novel therapeutic strategies aimed at reducing mitochondrial oxidative damage in PD.

Mitochondria and Neurodegeneration

Mitochondria are critical organelles for cell survival and normal development, since these organelles are the main modulators of cellular energy through the electron transport chain and ATP synthesis. They are also the main regulators of apoptotic death and aging and are involved in the control of calcium homeostasis and ROS production [28–31]. Various neurodegenerative diseases, such as AD, stroke, Huntington's disease (HD), and PD, are associated with mitochondrial disfunction, increased ROS production, and activation of apoptosis [31].

Currently, it is thought that the development of PD is either genetic or idiopathic. For example, several genes involved in its etiopathogenesis have been identified, and these include *PARK8*, *PARK2*, *PARK7* (DJ-1), *PINK1*, and *SNCA*, which encode for parkin and α-synuclein that accumulate in Lewy plaques or bodies in dopaminergic neurons [1, 5]. Some of these proteins, LRRK2, PINK1, and PARK7, are also involved in the regulation of mitochondrial functions (Fig. 1) like the maintenance of mitochondrial membrane potential ($\Delta\Psi m$) and the production of reactive oxygen species (ROS) and are thus affected during PD development [32, 33]. Likewise, it has been suggested that the response to unfolded proteins (UPR) is also involved in the development of PD [34–36]. In this case, increased ROS (reactive oxygen species) levels and imbalance in calcium levels that occur during the PD onset lead to an increase in the accumulation of misfolded proteins, including α-synuclein, which in turn induces the activation of regulatory proteins of the UPR such as PERK kinase, inositol 1α-dependent enzyme (Ire1α), transcription factor 6α (ATF6α), and the chaperone GRP78/Bip [34–37].

Various studies have shown that the production and accumulation of cytotoxic factors produce degenerative alterations in neurons [38–41]. Neurotoxicity has been attributed to high levels of ROS, nitric oxide, interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α), which can affect mitochondrial energetic processes in dopaminergic neurons and as consequence the activation of apoptotic pathways (Fig. 1) through a mechanism dependent on cytochrome c and caspase 3 [40]. Similarly, environmental and occupational factors have been shown to explain the rise in PD prevalence. Some of which include exposure to pesticides and herbicides (including rotenone and paraquat) by agricultural workers, and other factors include genetic environmental interactions, dietary factors such as consumption of polyunsaturated fatty acid, UPR, or the composition of the intestinal microbiome [36, 39, 42]. For these reasons, maintenance of mitochondrial properties in neurons and astrocytes are of main importance during brain injury and neurodegeneration (Barreto et al. 2011).

Astrocytic Functions: Interactions Between Neurons and Astrocytes in PD

Astrocytes are the most common type of cells in the brain of mammals and make up the glia along with oligodendrocytes and microglial cells [43]. These cells are organized in a syncytial network and are strongly communicated with each other and, in turn, with other cells such as pericytes, endothelial cells, and neurons [44]. Astrocytes (Fig. 2) are fundamental for processes such as the development and/or maintenance of the blood-brain barrier, promotion of neurovascular coupling, recruitment of cells through the release of chemokines, release of gliotransmitters, regulation of calcium levels, release and transport of glutamate by calcium signaling through the glutamate aspartate transporter (GLAST) and excitatory amino acid transporter (EAAT), maintenance of the general metabolism of the brain, control of cerebral pH, uptake of GABA (γ-aminobutyric acid) by specific transporters, and production of antioxidant enzymes [45–48]. During brain damage (e.g., oxidative stress), these processes are temporarily or permanently affected and the consequent impact on neuronal cells can lead to pathological conditions and neurodegenerative diseases [45, 46]. In this regard, it is important to note that neurons are more susceptible to injury than astrocytes since they have a lower antioxidant capacity and require a greater deal of metabolic coupling with astrocytes to combat oxidative stress [45]. Both under normal circumstances and after brain injury, astrocytes provide neurons with antioxidant protection, neurotrophic factors, substrates for neuronal metabolism, and glutamate reuptake [28, 49]. Although astrocytes are generally more resistant than neurons during traumatic or degenerative insult, these cells can also suffer severe damage which will result in increased neuronal death [49].

Astrocytes respond to most types of brain insults (infections, traumas, ischemia, oxidative stress, and neurodegenerative stimuli) by a process called reactive astrogliosis [50–52]. This process involves both morphological and molecular changes (Fig. 2) including increases in the expression of glial fibrillary acid protein (GFAP), vimentin, nestin and RhoA, glutamate uptake, protection against oxidative stress through the production of glutathione, neuroprotection by the release of adenosine, degradation of beta-amyloid peptides, regulation of the blood-brain barrier, and formation of glial scars. It is noteworthy that in some cases, reactive astrocytes can release inflammatory cytokines including tumor necrosis factor (TNF) and ROS [45, 53–57].

In the case of PD, there is conflicting information regarding the role of astrogliosis during disease onset. Some studies have shown that an increase in number of reactive astrocytes

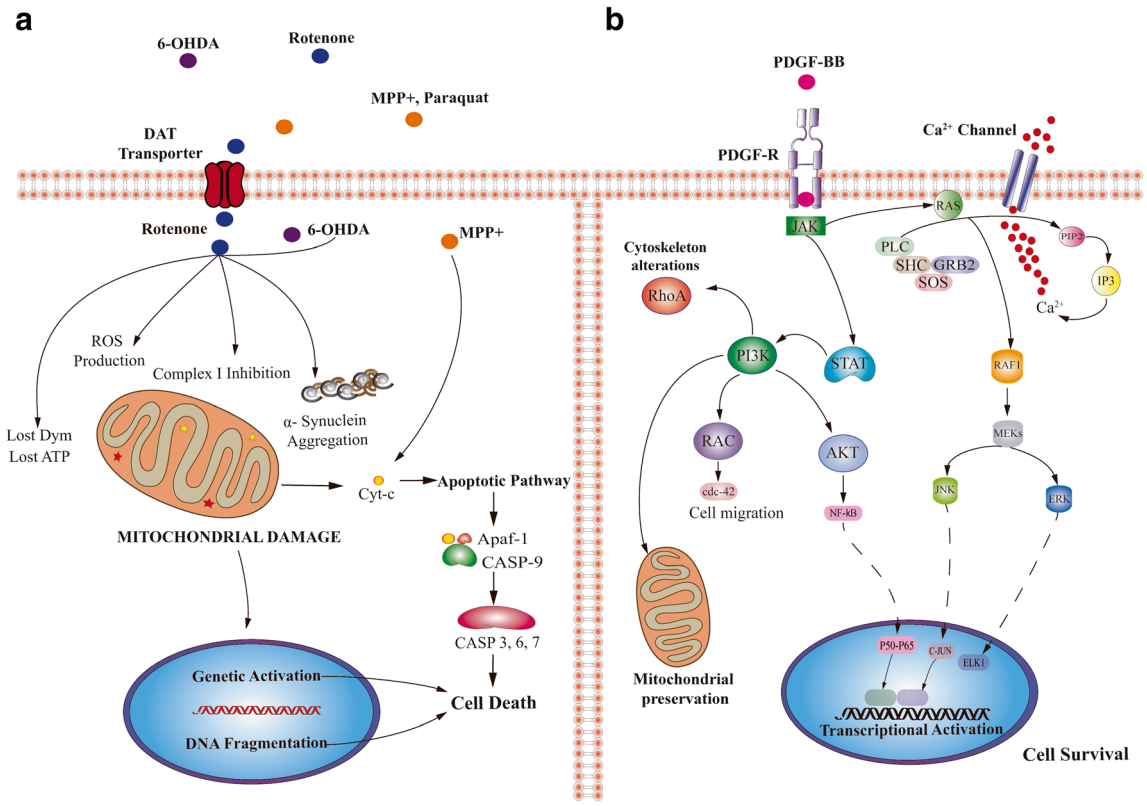

Fig. 2 Rotenone and PDGF-BB effects in experimental models of PD. Various toxins have been used as experimental models in PD including paraquat or rotenone and neurotoxins such as 6-hydroxydopamine (6-OHDA) and MPP+. Paraquat, 6-OHDA, and MPP+ use the dopamine transporter (DA) to enter the dopaminergic neurons, whereas rotenone due to its lipophilic structure does not require this transporter. These toxins can induce cellular and molecular alterations including the inhibition of mitochondrial complex I, formation of aggregates of α-synuclein, decrease in ATP production, ROS overproduction, and release of pro-apoptotic molecules such as cytochrome c. In turn, this molecule, in the cytosol, activates caspase 9 and triggers the canonical apoptotic activation in dopaminergic neurons (**a**). PDGF-BB decreases the damaging effects induced by rotenone at various levels, including modulation of intracellular calcium uptake, attenuated ROS production, regulation of morphological changes, mitochondrial protection, and activation of transcription factors such as NF-κB, thus overexpressing neuroprotective molecules such as neuroglobin. Furthermore, neuroglobin (ngb1) has protective actions on mitochondria by controlling oxidative stress production (**b**)

is indicative of the importance of these cells in the repair of dopaminergic neurons [58, 59], while other studies have shown that the presence of reactive astrocytes in postmortem tissues of patients with PD is quite low [60, 61], the latter suggesting that excessive accumulation of α-synuclein could suppress the protection exerted by astrocytes. Therefore, it is necessary to carry out additional studies on astrocytic activation in the context of the development of PD, including clinical trials. On the other hand, different biological or environmental toxins have been used, especially herbicides and pesticides such as rotenone, paraquat, or MPTP in PD models, since these compounds can induce astrocyte reactivity and microgliosis, as well as neuronal death, mitochondrial dysfunction, oxidative stress, and nuclear fragmentation [62–67]. All these processes resemble what happen during the initial stages of PD [39]. The rotenone model of PD is discussed in more details in the next section.

The Rotenone Model of Parkinson's Disease

Rotenone is a highly lipophilic flavonoid extracted from the roots of the plants belonging to the genus *Derris* and *Lonchocarpus* of the Leguminosae family [68]. This molecule is well known as an insecticide, and its main mode of action is through the inhibition of electron transport in the mitochondrial complex I where it blocks the production of ATP, consequently affecting cellular metabolism [39, 69]. The immediate inhibition of the mitochondrial respiratory chain leads to an increase in the production of ROS such as hydrogen peroxide and superoxide radical together with the peroxidation of cell membrane and DNA damage [1, 5, 29, 69, 70]. The cellular and molecular effects caused by rotenone include the selective degeneration of the nigrostriatal dopaminergic system, activation of astroglia and microglia, formation and accumulation of an altered form of α-synuclein and Tau proteins associated with dopaminergic neuron damage (Fig. 2), stress of endoplasmic reticulum (UPR), overexpression of chaperones

(GRP78), alterations in axonal formation associated with decreased activity of Cdc42 and Rac, and activation of apoptotic pathways mediated by BAD and caspases 3 and 9 [1, 5, 39, 68, 71–76]. Likewise, it has been determined that rotenone can act independently of its inhibitory effects on complex I, for example, rotenone affects the stability of microtubules, inhibits the expression of connexin 43 and gap junction permeability in astrocytes, disturbs calcium homeostasis, and induces DNA damage or inflammatory responses and disruptive effects on cell cycle [77–79].

As a neurodegenerative model, rotenone has been used successfully in in vitro and in vivo studies of PD, due to the similarity between the cellular and molecular effects produced by this toxin and the symptoms of PD [39, 62, 63, 80]. For example, rotenone has been previously used in cell lines such as SH-SY5Y (human neuroblastoma) and animal models of PD [1, 5, 39, 62, 80]. In this regard, it has been reported that in mice and rats, continuous administration of rotenone mimics some of the characteristics of PD, including selective degeneration of dopaminergic neurons, mitochondrial dysfunction and increased ROS production, astrocyte and microglial activation, blood-brain barrier dysfunction, formation of neuronal cytoplasmic inclusions, anxiety-like behavior, defects in spatial memory, and motor disorders [1, 5, 39, 72, 73, 81–85]. Finally, in a study by the National Institute of Health (NIH), it was observed that people with exposure to rotenone are 2.5 times more likely to develop PD than those who are unexposed [80], and the use of gloves and other protective measures is important to prevent exposure to this pesticide [86]. Together, collected data suggest the relevance of using rotenone as a neurotoxic compound for assessing cell damage in neurodegenerative events. Along with rotenone, other compounds have been used in the experimental study of PD in both cellular and animal models (Fig. 2). These compounds include 6-OHDA (6-hydroxydopamine), the pesticide paraquat (N,N′-dimethyl-4,4′-bipyridinium dichloride), and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a secondary metabolite produced from the synthesis of heroin [24, 38, 41, 87, 88].

Growth Factors and Neuroprotection

Several neurotrophic factors have been shown to protect neurons and glial cells against excitotoxicity and other neurodegenerative processes. For example, BDNF protects neurons against excitotoxicity by activating the transcription factor NF-κB, which induces the expression of antioxidant enzymes such as Mn-SOD, glutathione reductase, the anti-apoptotic protein Bcl-2, and the inhibitors of apoptosis proteins (IAP; [16, 89]). Likewise, administration of BDNF has been reported to protect neurons in the substantia nigra against 6-OHDA and MPTP in parkinsonian models of mice and primates [17].

Another study has demonstrated that VEGF expression is upregulated in rat brain after treatment with 40 nM rotenone, an effect that is accompanied by an increase in neuronal survival [14]. The basic fibroblast growth factor (bFGF) protects cortical and hippocampal neurons against the toxicity of glutamate by changing the expression of NMDA receptors and antioxidant enzymes such as superoxide dismutase (SOD) and glutathione reductase [16]. Similarly, it has been reported that pretreatment with bFGF decreases rotenone-induced apoptosis in human neuroblastoma cells (SH-SY5Y) by the activation of ERK1/2 and phosphatidylinositol 3-kinase (PI3K) [90]. On the other hand, the glial cell line-derived neurotrophic factor (GDNF), secreted by astrocytes, increases neuronal dopaminergic resistance to 6-OHDA toxicity, indicating a role of this growth factor in neuroprotection [91]. Likewise, insulin-like growth factors (IGFs) can protect neurons against excitotoxicity in both in vitro and in vivo models through the activation of PI3K/Akt pathway [16, 92, 93]. In this aspect, it has been reported that IGF-I affects glucose metabolism in astrocytes and neurons in the adult brain through increased expression of transporters GLUT3 and 4, and thus boosting glucose uptake that can exert neuroprotective and antiapoptotic effects [92]. More recently, it has been shown that combined treatment with stem cell factor (SCF) and granulocyte colony-stimulating factor (G-CSF) was able to improve several neurobehavioral parameters such as spatial learning and memory, posttraumatic anxiety, and risk-taking behavior in C57BL mice with traumatic brain injury (TBI) [94]. Moreover, the secretome of HEK-293 cells was used to reduce kainic acid neurotoxicity in murine hippocampal neurons through the activation of PI3K pathway and free radical scavenging mechanisms [95].

Other studies have used transplants of dopaminergic neurons or glial precursor cells in injured regions of the brain to increase the expression of growth factors such as BDNF, GDNF, and IGF, thus exerting a restorative effect [8, 96, 97]. For example, a study by Proschel et al. (2014) showed that the transplantation of glial precursor cells in rats injured with 6-OHDA caused the recovery of the DA neurons of the striatum together with an increase in the levels of GSH, GDNF, and BDNF [97]. Similarly, in our research group, the conditioned medium of mesenchymal stem cells was used to protect against oxidative injury induced by glucose deprivation in T98G astrocytic cells probably due to the presence of the growth factors, VEGF, IGF, PDGF-BB, and bFGF, in the conditioned medium [11, 98].

Platelet-Derived Growth Factor

PDGF is a homodimeric protein with approximately 30 kDa belonging to the family of PDGF/vascular endothelial growth factor (VEGF). Thus far, five dimeric compositions or isoforms have been identified: PDGF-AA, PDGF-BB, PDGF-

AB, PDGF-CC, and PDGF-DD [99, 100]. These five dimeric isoforms of PDGF show different affinities to the two tyrosine kinase receptors of PDGF, PDGFRα, and PDGFRβ [101–103]. As in the case of most tyrosine kinase receptors, binding of the ligand and subsequent dimerization of the subunits promotes reciprocal phosphorylation of tyrosine residues in the intracellular domain of the receptor [99, 104]. The tyrosine kinase receptors PDGFRα and PDGFRβ have a common structure with five extracellular immunoglobulin (IG)-type domains and an intracellular tyrosine kinase domain. This structure is shared with other receptor proteins such as c-Kit, c-Fms, and Flt [99, 105]. Once the receptor is phosphorylated, several signaling pathways and mediators can be activated, including mitogen-activated protein kinase (MAPK), PI3K, Wnt pathway, and phospholipase C (PLC). Additionally, it has been reported that different ligands of PDGF can induce the activation of transcription factors such as Nrf2 (nuclear factor (erythroid-derived 2)-like 2), STAT, ELK-1, c-jun/c-fos, HIF-1α, and NF-κB [99, 102, 106–110].

It has been established that PDGFRα and PDGFRβ receptors have different functions in the organism following their activation [99, 111]. PDGFRα is involved in the control of gastrulation and the development of the lung, intestines, skin, testes, and kidney, while PDGFRβ signaling plays important roles in early hematopoiesis and formation of blood vessels [111]. Current evidence shows that both homodimers and AB heterodimers can be generated, which bind with differential affinity to the receptors of the PDGF system (Andrae, 2008). PDGF-AA and PDGF-CC dimers bind to PDGFRα while PDGF-BB shows a greater affinity for PDGFRβ, though it can also bind PDGFRα since this receptor has a greater structural promiscuity [99, 104]. On the other hand, PDGF-BB is an important mitogenic factor produced by different cell types such as platelets, megakaryocytes, fibroblasts, smooth muscle cells, neurons, oligodendrocytes, and astrocytes [100, 108, 112–116]. It has been found that PDGF-BB induces embryonic and vascular development, in vivo wound healing as well as regulation of chemotaxis, and cell transformation processes in vitro [99, 100].

PDGF-BB and Protective Mechanisms

The signaling mechanisms involved in the protective effects of PDGF-BB include the activation of antiapoptotic and survival pathways, such as MAPK, PI3K-AKT, JNK, and NF-κB [109, 117, 118]. In this regard, it has been shown that the activation of these signaling pathways is dependent on the influx of calcium into the cell, which affects the phosphorylation of GSK3β and β-catenin [21, 66]. Likewise, it has been suggested that PDGF-BB can activate mechanisms involved in the modification of the cytoskeleton and cell migration through phosphatidylinositol 3,4,5, which then activates the Rac GTPase protein of the Rho family, the latter being involved in the modification of the actin cytoskeleton and morphological changes [119–121]. Additionally, it has been reported that treatment with PDGF-AB in injured fibroblasts increases the mitochondrial volume and the surface area of the crista ridges, suggesting that PDGF-AB can induce ultrastructural changes related to an increment in energy requirements, such as those produced during recovery from injuries [122]. Another signaling mechanism activated by PDGF ligands is mediated by the transcriptional activator STATs, which are important in processes such as proliferation, differentiation, survival, and cell transformation [108, 123]. The activation of STAT 1, 3, and 6 by PDGF ligands has been observed in vascular muscle cells in processes such as airway remodeling in patients with asthma [123]. This activation is apparently dependent on the production of H_2O_2 as a result of the activation of the transmembrane NOX enzyme (NADPH oxidase/dual oxidase enzyme), which is independent of ROS production by mitochondria [108, 123]. However, the involvement of different isoforms of PDGF in the production of ROS in the nervous system has neither been established, nor what the effects would be during this process. It is possible that production of hydrogen peroxide by PDGF ligands has beneficial effects as this is a second messenger in signaling pathways activated by the STATs, and is also involved in the regulation of downstream phosphatase proteins [108, 123, 124].

It has also been suggested that PDGF-BB can activate the NF-κB transcription factor by regulating the PI3K/AKT pathway during cell growth, differentiation, apoptosis, and stress response, also decreasing the expression of genes such as matrix metalloproteinase 9 (MMP-9) and VEGF [109, 117]. On the other hand, the activation of PI3K/AKT leads to the inactivation of the kinase GSK3β. In its inactivated form, GSK3β prevents the degradation of β-catenin, increasing its accumulation in the cytoplasm and causing its translocation to the nucleus, where it can contribute to the activation of genes associated with cell survival [21]. Additionally, β-catenin is related to mitochondrial homeostasis, regulation of ATP production, and lipid oxidation [125, 126]. Likewise, Avila-Gómez et al. (2010) showed that IGF-I protects human lymphocytes by activating PI-3K/AKT, regulating p53, and maintaining $\Delta\Psi m$ [127]. Considering that IGF-I induces the activation of β-catenin by PI-3K/AKT [128], this activation could lead to a subsequent mitochondrial protection. In this aspect, previous studies in neuronal models have also shown that 24 h of pretreatment with PDGF-BB exerted significant protection against hydrogen peroxide, glucose deprivation, and excitotoxicity damage in cultured neurons [118, 129, 130]. Alternatively, it has been shown that PI3K/AKT exerts a negative regulation on the transcription factors FOXO (forkhead transcription factors), which are involved in cell survival, regulation of oxidative stress, and polarization of the mitochondrial membrane [131, 132], suggesting the importance of the PI3K/AKT pathway in these cellular events.

It has been suggested that different isoforms of PDGF possess important neuroprotective and regenerative functions in several research models [13, 18, 20–22, 114]. For example, increases in the PDGF-AA and PDGF-BB ligands and PDGFRα and PDGFRβ receptors have been observed in cerebral samples from patients with ischemia [114, 133]. It was also shown that pretreatment with 120–240-ng/mL doses of PDGF-BB decreased the death of pyramidal neurons in rats during ischemic damage [20]. Likewise, it was determined that intracerebral administration of PDGF-BB decreased the lesion area due to overstimulation with NMDA in neonatal rats [134]. On the other hand, it has been reported that PDGF-CC protected murine neuronal cells against apoptotic death induced by different types of toxins including 6-OHDA and HIV TAT toxin [21, 22]. In recent years, Zachrisson et al. (2011) suggested restorative effects of PDGF-BB in dopaminergic neurons of rats injured with 6-OHDA and MPTP [18], and clinical trials in humans performed by the same group [13] did not produce adverse effects. Similarly, a recent study by Osborne et al. (2018) showed that PDGF-AB produced by human mesenchymal stem cells (hMSC) reduced optic nerve injury in human explants [135]. Moreover, it was recently observed that PDGF-BB used as pretreatment (200 ng/mL) was able to protect human astrocytic cells T98G against rotenone (50 μM) via reducing the production of superoxide and peroxide radicals, maintenance of Δψm (mitochondrial membrane potential) and mitochondrial ultrastructure, and activation of the PI3K/AKT signaling pathway [136–138].

Another important aspect of PDGF-BB is its ability to modulate cell morphology. In this regard, it has been shown that PDGF-BB induces lamellipodia formation and increases fibroblast motility mediated by rearrangements of actin fibers, these processes being dependent on PI3K kinase [139, 140]. It has also been observed that the expression of the PDGFRβ receptor is necessary for the development of the embryonic neural crest, astrocytic development and differentiation, and the morphogenesis and plasticity of dendritic spines [113, 141]. Indeed, growth factors such as PDGF-BB and VEGF induce the activation of RhoA protein in endothelial cells during the angiogenesis process [121, 142]. In the case of astrocytes, the inactivation of RhoA by clostridium botulinum C3 toxin induces irreversible changes in the cytoskeleton, therefore generating a star-shaped astrocyte morphology associated with the disassembly of actin and intermediate filaments [143]. Likewise, it has been pointed out that increase of peroxides and nitric oxide causes the activation of Rho/ROCK in vascular models [144, 145]. In this aspect, Fujimura and Usuki (2012) found that exposure to 100 nM rotenone or inorganic mercury inhibited the expression of the protein CDC42 and Rac1 without affecting the expression of RhoA, together with axonal degeneration and cortical brain cell death [146]. Likewise, it has been demonstrated that pharmacological inhibition of ROCK kinase decreases the phosphorylation of ERK1/2, even after stimulation with PDGF-BB in glioblastoma cells [147].

Several studies have suggested that PDGF-BB signaling is regulated in part by intracellular calcium concentration, both in normal and pathological conditions [21, 148–150]. In this regard, it has been determined that PDGF-BB also activates phospholipase C causing the formation of inositol triphosphate (IP3) and diacylglycerol (DAG), which increases the mobilization of Ca^{2+} from intracellular compartments and leads to the activation of protein kinase C [149, 150]. Additionally, PDGF-CC protects against TAT toxin from HIV by activating the transient potential channel 1 (TRPC) channels, which modulates the downstream protein pathway such as GSK3β [21], in the SH-SY5Y neuroblastoma line. These studies suggest that the PDGF family of growth factors, especially PDGF-BB, might have important neuroprotective properties. The protective mechanisms activated by PDGF-BB in the brain are summarized in Fig. 2.

Neuroglobin Activation by Growth Factors

In recent years, the neuroglobin protein (ngb1) has been assessed in both neurons and astrocytes due to its multiple functions relevant to neuroprotection in pathologies such as focal ischemia, AD, apoplexy, and traumatic brain injury [10, 151–154]. Ngb1 has 150 aa and a molecular weight of 18 kDa, containing a heme group which allows it to transport and store oxygen in different organs such as the retina and the brain [155]. It has been suggested that this protein has other functions such as signaling during hypoxia, serving as NADH oxidase, elimination of ROS, regulation of calcium levels, mitochondrial regulation, and neuroregeneration following optic nerve injury in mice [151, 156–159]. At the genetic level, it has been observed that the gene promoter region of neuroglobin can be regulated by transcription factors such as hypoxia-inducible factor 1-α (HIF-1α), SP1, CREB, and NF-κB, which are related to cellular response to hypoxia [160–162]. However, the most studied function of neuroglobin is adaptation to hypoxia which has been studied in various animal models and cell lines [151, 163, 164]. In this aspect, it is known that under normoxic conditions neuroglobin is bound to oxygen, while under hypoxic conditions, this protein adopts a hexacoordinated structure of the heme group. This hexacoordinated structure allows rapid transfer of electrons between ferrous neuroglobin and ferric cytochrome during hypoxia. Hence, by rapidly reducing ferric cytochrome c, non-apoptotic levels of ferrous cytochrome c would be maintained, which would decrease apoptotic activation, thus exerting a potentially neuroprotective effect [164–166]. Likewise, it has been shown that neuroglobin overexpression increase the antiapoptotic signaling and the reduction of movement disorders in transgenic models of mice in conditions of hypoxia and ischemia [167, 168].

It has been reported that neuroglobin can be translocated to the mitochondria, where it interacts with proteins such as the Atp1b1 and Atp1b3 subunits of Na^+/K^+ ATPase, cytochrome1 (Cyc1), electron-transfer-flavoprotein, alpha polypeptide (Etfa), and voltage-dependent anionic channel (VDAC), suggesting its importance in mitochondrial protection [169, 170]. Interestingly, neuroglobin silencing by siRNA impairs $\Delta\psi m$ maintenance and leads to increased ROS levels in both astrocytes and neurons [10, 151, 171]. Likewise, it has been suggested that neuroglobin could regulate mitochondrial calcium levels in human neuroblastoma SH-SY5Y cells, which might also be related to a decrease in the activation of apoptotic pathways [157, 172]. Finally, it has been recently shown that neuroglobin is able to protect mitochondria against MPP+ treatment in neuroblastoma SK-N-BE2 cells through its association with lipid raft complexes [173].

Several conditions are known to be involved in the regulation and expression of neuroglobin. These include hypoxia and ischemia, glucose deprivation, hormonal treatments, vascular endothelial growth factor (VEGF) and the use of conditioned medium of mesenchymal stem cells derived from human adipose tissue [10, 11, 151, 164, 170]. For example, it was observed that VEGF stimulated the expression of ngb1 in cortical neuronal cultures of embryonic mice through activation of the VEGFR2/Flk1 receptor [174]. It was also shown that both transforming growth factor-β1 (TGFβ1) and PDGF-BB increased the expression of the cytoglobin protein in hepatic stellate cells [175]. Finally, it was reported by our group that PDGF-BB increases GPx1 and neuroglobin expression in an astrocytic model during rotenone insult [138], suggesting the importance of PDGF-BB and other growth factors in neuroglobin modulation.

Conclusions

Previous studies have demonstrated the protective effects of PDGF-BB and other growth factors in neurons and astrocytic cells against oxidative stress. In this aspect, PDGF-BB was shown to improve mitochondrial protection at the functional level by activating proteins such as neuroglobin and GPx1. Hence, the available evidence suggests that PDGF-BB-induced signaling pathways may be relevant for the preservation of mitochondrial function. Additional studies in astrocytic primary cultures, in vivo models, and extended clinical trials are needed to clarify the underlying mechanisms and molecular signature through which PDGF-BB interacts with mitochondria and confers protection to astrocytes and neurons. It is also important to establish which proteins might be interacting with neuroglobin within mitochondria in order to better decipher this protective mechanism of PDGF-BB against oxidative stress.

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Compliance with Ethical Standards

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

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