The potential of mitochondrial modulation by neuroglobin in treatment of neurological disorders

Armita Mahdavi Gorabi a,1, Saeed Aslani b,1, George E. Barreto c,d, Eliana Báez-Jurado e, Nasim Kiaie a, Tannaz Jamialahmadi f,g, Amirhossein Sahebkar b,1,3,4,5

a Research Center for Advanced Technologies in Cardiovascular Medicine, Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran
b Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
c Department of Biological Sciences, University of Limerick, Limerick, Ireland
d Health Research Institute, University of Limerick, Limerick, Ireland
e Departamento de Química, Facultad de Ciencias, Universidad Antonio Nariño, Bogotá D.C., Colombia
f Department of Food Science and Technology, Quchan Branch, Islamic Azad University, Quchan, Iran
g Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

ABSTRACT

Neuroglobin is the third member of the globin family to be identified in 2000 in neurons of both human and mouse nervous systems. Neuroglobin is an oxygen-binding globin found in neurons within the central nervous system as well as in peripheral neurons, that produces a protective effect against hypoxic/ischemic damage induced by promoting oxygen availability within the mitochondria. Numerous investigations have demonstrated that impaired neuroglobin functioning is implicated in the pathogenesis of multiple neurodegenerative disorders. Several in vitro and animal studies have reported the potential of neuroglobin upregulation in improving the neuroprotection through modulation of mitochondrial functions, such as ATP production, clearing reactive oxygen species (ROS), promoting the dynamics of mitochondria, and controlling apoptosis. Neuroglobin acts as a stress-inducible globin, which has been associated hypoxic/ischemic insults where it acts to protect the heart and brain, providing a wide range of applicability in the treatment of human disorders. This review article discusses normal physiological functions of neuroglobin in mitochondria-associated pathways, as well as outlining how dysregulation of neuroglobin is associated with the pathogenesis of neurodegenerative disorders.

1. Introduction

Neurological damage, such as brain trauma or cerebral stroke, is associated with high mortality and intense chronic disability throughout worldwide population [1,2]; such disorders significantly reduce a patient’s quality of life and life expectancy. Nonetheless, there has been little success in developing effective treatments to improve post-trauma recovery. Current treatments for neurodegenerative disorders aim to reduce the severity of the symptoms with little effect on halting disease progression [3].

Stimulation of endogenous neuroprotective mechanisms has been investigated as a possible approach for devising therapies to treat neurological complications. In addition, administration of these neuroprotective compounds may also confer beneficial effects. One possible key target is neuroglobin, a vertebrate globin family involved in cellular oxygen homeostasis [4]. Neuroglobin is primarily expressed in the central nervous system (CNS), and is located in the cytoplasm, inside mitochondria, nucleus and subcellular cell cytoplasm. Among the different brain areas, the hypothalamus has been attributed with the highest expression of neuroglobin [5]. The function of neuroglobin is to promote the cell viability during hypoxia as well as oxidative stress. Therefore, Studies have reported a neuroprotective function for

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neuroglobin, as its expression is negatively associated with the intensity of histological complications and functional impairments in patients with stroke and neurodegenerative disorders in in vitro studies and animal experiments [6,7]. Nevertheless, there is little data with respect to the mechanisms underlying the neuroprotective role of neuroglobin [8]. A number of hormones like vessel endothelial growth factor (VEGF) can induce the production of neuroglobin, suggesting another approach to increase the production of neuroglobin for the therapeutic purposes [9].

The mitochondria are involved in several vital cellular processes, including homeostasis of calcium, energy supply, redox signaling, production of ROS and programmed cell death [10,11]. Neuronal cells, especially, rely on effectively functioning mitochondria to maintain the high energy demand of the brain [12]. Impaired mitochondrial functioning has been associated with numerous diseases of CNS, including Alzheimer’s disease, Huntington disease, and Parkinson’s disease [13,14]. Previous studies have demonstrated that neuroglobin is expressed in cells that have active metabolism and depend on oxygen consumption [15]. As a consequence, there might be a functional association between mitochondrial function and neuroglobin level in cells. This review will discuss the neuroprotective actions of neuroglobin in mitochondrial regulation, as well as outline how neuroglobin could be used to improve our understanding of the pathogenesis of neurological disorders, stroke, and hypoxia and contribute to designing novel therapeutics for such disorders.

1.1. Evidence of neuroglobin-mediated neuroprotection

Numerous investigations have indicated that neuroglobin plays a neuroprotective role in multiple neurological diseases (Fig. 1). In vitro experiments have demonstrated that knockdown of neuroglobin results in increased vulnerability of cortical neurons to hypoxia [16]. Conversely, overexpression of neuroglobin produces significant protection against hypoxia in the neurons in vitro [16]. Similarly, enhanced overexpression of neuroglobin (approximately 100-fold increase) in a neuroblastoma cell line protected the neurons against oxygen/glucose deprivation (OGD) conditions [17,18]. Overexpression of neuroglobin in a neuroglobin-transgenic mouse stroke model ameliorated the intensity of clinical disease course, and improved histological, as well as functional impairments [19]. Additionally, neuroglobin knockdown in rats exacerbated the manifestations of focal cerebral ischemia in the animals [7]. In vivo experiments using double transgenic mice for neuroglobin and amyloid precursor protein (APP) suggested that neuroglobin overexpression plays a protective role against β-amyloid-induced neurotoxicity, as well as Alzheimer’s disease pathogenesis [20]. In this regard, overexpression of neuroglobin in transgenic mice resulted in protection of retinal ganglion cells against glaucomatous damage and ocular hypertension [21]. With respect to several protective mechanisms by neuroglobin, such as ROS scavenging and ATP conservation, strategies aiming to upregulate of neuroglobin expression may offer a potentially effective therapeutic approach for the treatment of neurodegenerative diseases [22].

According to the available evidence, the neuroprotective mechanism of neuroglobin is a consequence of modified mitochondrial functioning, such as reduced ROS production, improved ATP generation and altered cell death signalling, which will be discussed in the following sections.

1.2. ROS production in mitochondria and neuroglobin

Evidence show the involvment of neuroglobin in the production of reactive nitrogen species (RNS) and ROS [23]. Production of ROS occur at the termination of mitochondrial respiration, in which complex I and III transfer electrons to oxygen resulting in the production of superoxide anions [24]. Higher amounts of superoxide anions are generated when the electron carriers bear extra electrons, including disorders in which oxidative phosphorylation is prevented. It has been reported that neuroglobin is involved in scavenging the NO species, as well as ROS. Overexpression of neuroglobin in the neuroglobin transgenic mouse significantly decreased the production of superoxide anion upon hypoxia/reoxygenation in the cortical neurons compared to wild-type mice [25]. Neuroglobin has the ability to bind to NO [26] which helps to protect against NO-induced neurotoxicity [27], demonstrating that neuroglobin plays a critical role in neutralizing the

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**Fig. 1. Effects of neuroglobin (Ngb) in neuronal cells.** The beneficial effects of Ngb has been reported not only at the structural level but also on cell organelles. (A) Cellular alterations have been found in different brain pathologies, these include condensation of actin filaments and microtubules, mitochondrial aggregation and increased release of calcium (Ca\(^{2+}\)) from the reservoir of the endoplasmic reticulum (ER), leading to the uptake of this ion by the mitochondria to cause mitochondrial dysfunction. Mitochondrial dysfunction involves damage to mitochondrial membranes, degradation and release of Cytochrome c (Cyt c), thus producing more calcium (B) Beneficial effects of Ngb favoring transitory mitochondrial movement and enhanced ATP production. Ngb has been found to be associated with the regulation of calcium channels at the cellular level, especially on the ER, with a positive impact on reducing calcium release, which favors the maintenance of Cyt c within the mitochondrial intermembrane space and prevents the release of apoptosis inducing factor (AIF) while maintaining cell survival. Another effect that has been reported is the effect of Ngb on cell signaling pathways, such as that of Akt, a protein that can be phosphorylated by Ngb, favoring reduced apoptosis. Ngb also has the ability to trigger mitoATP receptor activity, which stimulates the reduction of reactive species such as H\(_2\)O\(_2\) with a consequent decrease in oxidative cell damage.

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neuroprotective effects of neuroglobin. Additionally, overexpression of neuroglobin in the neuroglobin transgenic mouse with ischemia-reperfusion injury was shown to be correlated with decreased ROS/RNS generation, as well as reduced lipid peroxidation and injury rate in the CA1 region of the hippocampus [28]. Nonetheless, the exact mechanisms underlying this effect has not been found. It may be attributed to the direct binding of neuroglobin to ROS/RNS or the interaction of neuroglobin with the components of the mitochondrial respiration chain, such as mitochondrial complex III [22,29], as well as indirectly improving mitochondrial functioning. Using recombinant humanized neuroglobin, Li et al. (2011) reported that neuroglobin possesses a direct antioxidant effect by scavenging multiple free radicals, such as hydrogen peroxide, superoxide anion, hydroxyl radical and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt radical cation [30]. Additionally, this study demonstrated that recombinant humanized neuroglobin had a limited ability to scavenge the superoxide anion, but this effect was better than GSH and comparable with vitamin C [36]. Further in vivo and clinical studies are required to determine whether neuroglobin could improve recovery post-stroke by enhancing the scavenging of free radicals and preserving neurological functioning.

1.3. Neuroglobin is involved in ATP generation within mitochondria

Studies have also demonstrated that neuroglobin closely interacts with mitochondria in addition to its cytoplasmic effects. Electron microscopy and immunocytochemistry studies have demonstrated that neuroglobin in neurons is located within the mitochondria, nucleus and subcellular cell cytoplasm [31]. Kanai et al. (2001) also revealed that neuroglobin in neurons is colocalized with nicotinic oxide synthase (NOS) enzyme, suggesting that neuroglobin directly interacts with the mitochondria [32]. Similar results were reported by Lechauve et al. (2012), where neuroglobin was localized inside the mitochondria of retinal neurons [33]. Moreover, in vitro experiments of cortical neurons indicated that only 10% of the total neuroglobin was localized in mitochondria [29].

In spite of neuroglobin’s ability to bind O2, the major function of neuroglobin might not be the transportation of O2 and delivering it to neurons. Neuroglobin has a high affinity for O2 but a low detachment rate, therefore, it is more likely that neuroglobin plays an important role in sensing O2 and maintaining energy metabolism of cells by conserving ATP levels [34,35]. Research has demonstrated that there is an association between stroke onset and ATP disturbances. Within the ischemic core area, the remarkable decrease in blood supply culminates in reduced glucose and O2 supply, hence, very little ATP is generated [36,37]. Dysregulation of ATP levels indicates disrupted oxidative metabolism in the mitochondria, resulting in lactate production [36]. Along with decreased ATP levels during ischemia, the respiratory capacity of mitochondria is significantly reduced in the penumbra area of brain, as well as within the core [38,39]. The respiratory capacity of mitochondria can be returned temporarily after reperfusion, but decreased gradually over time [40]. The release of cytochrome c (Cyt c) from the mitochondria, as well as oxidative stress are plausible mechanisms for impaired respiratory function in mitochondrial [41,42].

Overexpression of neuroglobin has been observed in the retina, specifically neuroglobin within photoreceptors is localized to the mitochondria where higher levels of oxygen in the retina are consumed [43]. In addition, research has indicated the involvement of neuroglobin in preserving the function of the mitochondria towards triggers such as DNA damage, increased calcium levels, low nutrient levels, receptor signaling, oxidative stress, and aggregation of misfolded proteins [44]. Transfection of PC-12 cells with pcDNA3-neuroglobin enhanced cell survival and improved mitochondrial dysfunction following amyloid β administration [45]. Furthermore, chicken β-actin action promoter was used to increase the expression of neuroglobin in neuroglobin transgenic mice, resolving the aggregation of mitochondria induced by hypoxia and protected the neurons from apoptosis [46]. In vitro overexpression of neuroglobin in cortical neurons obtained from neuroglobin transgenic mouse resulted in amelioration of mitochondrial function. In addition, during the first stages of hypoxia/reoxygenation, neuroglobin overexpression resulted in attenuation of ATP levels [25]. In a similar way, transfection of SH-SY5Y cells with pDEST40-neuroglobin plasmid led to upregulation of neuroglobin expression which produced a remarkable attenuation of H2O2-induced oxidative stress and a promoted levels of intracellular ATP [47]. Additionally, increasing the expression of neuroglobin through transfection of human neuronal cells by pDEST40-neuroglobin plasmid promoted cell survival and prevented the reduction in ATP following hypoxia/reoxygenation [48]. On the contrary, knocking down neuroglobin appears to dampen mitochondrial function, leading to increased ROS and poorer cell survival rate when astrocytes and microglia are subject to metabolic dysfunction [9,49]. Most neuroprotective actions of neuroglobin on mitochondria are sought to happen through activation of estrogen receptors, as neuroglobin expression is upregulated when estradiol signaling is triggered [50,51]. Taken together these results demonstrate that neuroglobin plays an important role in conserving ATP generation in mitochondria. This can be implemented by either maintaining the general function of mitochondria or particular effect on mitochondrial respiration, requiring further studies for detailed clarification of the mechanism.

Neuroglobin is primarily found in the cell cytoplasm [52], where it plays a function as guanine-nucleotide-dissociation inhibitor (GDI) and modulate the cell signaling [53]. Research has identified that neuroglobin-binding proteins by yeast two hybrid assay indicated that neuroglobin binds to mitochondrial complex III subunit, namely cytochrome c1 [54]. Recently, it was disclosed that the negative charges on the neuroglobin’s surface play a role in its interaction with cytochrome c [55]. Functional evaluations indicated reduced activity of mitochondrial complexes I and III after neuroglobin knockdown [33]. Hence, it seems that by binding to mitochondrial respiratory complexes and influencing their functions, neuroglobin plays a key role in ATP generation. Several studies have confirmed the subcellular localization of neuroglobin and its interaction with mitochondria. Hundal et al. (2012) suggested that utilizing an anti-neuroglobin antibody is the most reliable approach to detect the subcellular localization and function of neuroglobin [56]. Conversely, neuroglobin-null mice model have now been introduced as the most reliable validating technique for future studies [57]. As a consequence, the previous results about the subcellular localization of neuroglobin through immunostaining need to be interpreted with caution.

1.4. Neuroglobin and apoptosis signaling in mitochondria

In addition to ROS scavenging and ATP generation, neuroglobin is involved in signaling mechanisms (Fig. 2). Ferric neuroglobin has the potential to bind to the guanosine diphosphate (GDP)-bound state of the G protein α-(Gαt) subunit, where it acts as a guanine-nucleotide dissociation inhibitor (GDI) [53]. The conversion of GDP to GTP is inhibited by ferric neuroglobin, preventing the Gαt subunit from binding to the Gβγ complex. This in turn triggers downstream signaling transduction, resulting in oxidative stress protection [58].

The intrinsic pathway of apoptosis is mediated by the mitochondria, where several pro-apoptotic and anti-apoptotic proteins are involved, including Bcl-2 and Bcl-xL, Bax, Bak, Bid, Bim, Bad and PUMA [59]. Upon disruption of the mitochondrial membrane, caspase-dependent and caspase-independent apoptotic pathways are activated due to the release of Cyt c and apoptosis-inducing factor (AIF) into the cytoplasm, respectively. From here, Cyt c binds to Apaf1 in cytoplasm, initiating the assembly of apoptosomes, leading to caspase 9 activation which stimulates caspase 3 and caspase 7 [60]. Secondly, in the caspase-independent apoptosis pathway AIF is transferred into the nucleus and modulates important steps of apoptosis, such as comprising of chromosome and fragmentation of DNA strands [61].
ROS produced in the mitochondria plays a role in signaling apoptosis. The primary data concerning the implications of mitochondrial ROS in apoptosis originated from studies about cell cytotoxicity induced by tumor necrosis factor (TNF) – α [62]. Research utilizing antioxidants or techniques for overproduction of ROS have established a vital role of ROS in apoptosis signaling [63]. As neuroglobin is involved in scavenging ROS, it is probable its involvement in controlling apoptosis signaling in neurons. In vitro neurons isolated from neuroglobin-transgenic mice resulted in downregulation of cell death triggers within the neurons, such as reduced aggregation of mitochondria and hypoxia-induced microdomain polarization [46]. Moreover, in vitro studies have also indicated that neuroglobin inhibits the intrinsic apoptosis pathway in human neuroblastoma SH-SY5Y cells by interrupting the activation of pro-caspase 9 by interacting with Cyt c [64]. Dai et al. (2019) demonstrated that increased neuroglobin expression in rats led to improved recovery following spinal cord injury. This was attributed to reduced apoptosis and lesions in the spinal cord tissues. Additionally, this study reported upregulation of caspase 3, Cyt c and bax levels, while reducing bcl-2 expression, within the spinal cord tissues [65]. Conversely, Chen et al. (2018) reported upregulation of bcl-2 and downregulation of caspase 3, caspase 9 and Bax when recombinant neuroglobin was administered in rabbits suffering from subarachnoid hemorrhage. This study also observed that TAT protein transduction domain facilitated the delivery of neuroglobin into brain neurons, leading to inactivation of the mitochondrial apoptotic pathway [66]. In addition, TAT-neuroglobin was indicated to protect the neuron-like cells from OGD-induced apoptosis by activating the Jak2/Stat3 pathway [67].

Opening of the permeability transition pore (PTP) on the mitochondrial membrane leads to the release of Cyt c into the cytoplasm [68], where caspase-dependent or caspase-independent apoptosis pathways are initiated. Upregulation of neuroglobin expression by transduction of mouse cortical neurons with AAV-neuroglobin was found to reduce the opening of mitochondrial PTP, leading to a decline in the release of Cyt c after OGD and reoxygenation [69]. Hence, it seems that neuroglobin plays a neuroprotective role against apoptosis by repressing the OGD-induced mitochondrial PTP opening. In addition to decreasing the release of Cyt c through inhibition of mitochondrial PTP opening, neuroglobin has been shown to improve cell survival through a variety of anti-apoptotic mechanism. Fago and colleagues (2006) demonstrated that neuroglobin plays a role in the redox reaction of ferric Cyt c to ferrous Cyt c [70], leading to apoptosis inhibition. This is because Cyt c is released from the mitochondria in the form of ferric Cyt c [71], and this form, but not ferrous Cyt c, is functional in stimulating apoptosis [72]. As a consequence, ferrous Cyt c produced by neuroglobin becomes non-functional and does not stimulate apoptosis. Bioinformatic evaluations have demonstrated that when neuroglobin binds to Cyt c the redox reaction aftermath inhibits the activation of caspase 9 [73]. Neuroglobin binding to Cyt c can also directly reduce the level of released Cyt c from mitochondria.

Calcium plays a central role in a variety of key cell signaling pathways, including apoptosis [74]. The endoplasmic reticulum (ER) is the main storage of calcium in cellular cytoplasm [75]. Calcium is involved in regulating mitochondrial morphology, as well as controlling molecules involved in apoptosis. Upon apoptotic signaling, ER releases calcium which is then absorbed by the mitochondria, leading to enhanced cytochrome c leakage from the mitochondria [76]. Released Cyt c binds to the inositol trisphosphate receptor (IP3R) on the ER, resulting in further calcium release, further enhancing the release of Cyt c from more mitochondria and stronger signaling of apoptosis [77]. By controlling cytoplasmic calcium concentrations, neuroglobin has been shown to regulate apoptosis in response to cell death triggers. Upregulation of neuroglobin expression using pDEST40-neuroglobin plasmid transfection of neurons was shown to inhibit the increment of cytoplasmic calcium level after hypoxia/reoxygenation [48]. Neuroglobin may control calcium levels by modulating transporters on the cell membrane or calcium channel on the ER membrane. In addition to regulating calcium levels, neuroglobin interrupts apoptosis by indirectly controlling the quality and quantity of apoptosis-related molecules. Research has shown that overexpression of neuroglobin following transfection of

![Fig. 2. Neuroglobin (Ngb) reduces oxidative damage and maintains optimal ATP levels in the brain.](image-url)
SH-SY5Y cells with pDEST40-neuroglobin plasmid led to Akt phosphorylation and activation of mitochondrial ATP-sensitive potassium (KATP) channel, shielding the cell against H₂O₂-induced injury [47]. Neuroglobin-induced phosphorylation of Akt prevents Cyt c and AIF release, resulting in apoptosis suppression [78]. Cell culture studies indicated that neuroglobin promotes Akt phosphorylation and plays a protective role in astrogial, due to inhibition of H₂O₂-induced oxidative stress and apoptosis [79].

Research has demonstrated that modulating apoptosis can produce neuroprotective effects in animal models [80]. Inhibition of caspase-3 and caspase-9 in rat/mice model of stroke improved brain tissue loss and ameliorated neurological outcomes [81-83]. With respect to neuroglobin’s potential to interrupt apoptosis in neurons, enhancing the expression of neuroglobin might provide a promising approach in the regulation of apoptosis in neurodegenerative diseases. Assessing the endogenous factors involved in the regulation of neuroglobin expression may lead to devising a therapeutic tool for treatment of brain diseases [22].

1.5. Neuroglobin and the mitochondrial dynamics

Mitochondrial dynamics involves continuous fusion and fission procedures which is critical for supplying the energy required for transportation and channel functioning. In addition, mitochondria undergo mitophagy, through which impaired and non-functional mitochondria are degraded in order to ensure continued functioning of quality mitochondrial systems. Neurodegenerative disorders have been characterized by impaired mitochondrial dynamics [84,85]. Considering the role of neuroglobin in the generation of ATP and mitochondrial energy production, as well as in mitochondrial aggregation upon hypoxia, neuroglobin may preserve mitochondrial dynamics [46].

In the fusion process of mitochondria the two dynamin-like proteins, Mfn1/Mfn2 and OPA1, are involved [86], whereas Fis1 and dynamin-related protein 1 (Drp1) are involved in fission of mitochondria [87]. Research has suggested that there is a correlation between impaired mitochondrial fission/fusion processes in neurodegenerative disorders because mitochondrial fission was seen to be an early event in diabetic neuropathy and ischemic stroke [88,89]. To apply this mechanism in therapeutics, Barsoum et al. (2006) demonstrated that overexpression of Mfn1 or knockdown of Drp1 gene led to suppressed mitochondrial fission, which in turn culminated in protection against NO-induced neuronal cell death [89]. Similarly, Liu and colleagues revealed that upon transient middle cerebral artery occlusion in mice there were downregulation of Drp1 and Opa1 in the ischemic core area, while both were upregulated in the ischemic penumbra [90]. These results imply fusion and fission of mitochondria was conserved in surviving ischemic penumbra.

Mobilization of mitochondria toward the subcellular locations like presynaptic terminals are required to supply energy to high demand regions [91]. Actin microtubules are involved in the transportation of mitochondria that are composed of dynein and kinesin, the ATP-dependent molecules involved in cellular movements [92,93]. Adaptor proteins, such as Miro1, Miro2, TRAK1 and TRAK2, are involved in modulating the indirect binding of kinesin to the mitochondria [94,95]. Synaptic activity and, hence, neuron viability depend on the movements and distribution of mitochondria in neuronal cells [96]. Cortical neurons in vitro have been shown to present with impaired transport and cell morphology following hypoxia/reoxygenation [97]. Proper and timely degradation of damaged or aged mitochondria is crucial for maintaining mitochondrial quality control. Mitophagy plays a key role in clearing the impaired and aged mitochondria to be replaced by newly developed organelles [98]. PTEN-induced putative kinase 1 (PINK1) and Parkin play vital roles in this mitophagy process [99-101]. Interestingly, ischemic preconditioning has been shown to trigger mitophagy by enhancing the transfer of Parkin into the mitochondria. This protective preconditioning effect was attenuated following knocking out of the Parkin gene [102]. Mitophagy has also been shown to be involved in the pathophysiology of neurodegeneration. In inherited axinias, upregulation of mitophagy resulted in degenerating of Purkinje neurons, implying that appropriate control of mitophagy is required to allow for proper functioning of neurons [103]. Taken together, neuroglobin by affecting on the generation of ATP and mitochondrial energy supply, and mitochondrial aggregation after hypoxia, it appears to play a role in the mitochondrial dynamics, suggesting its involvement in the neurological disorders.

Upregulation of neuroglobin prevents the aggregation of neurons following hypoxia [46]. Following Cyt c release from the mitochondria in presence of apoptosis-inducing signals, mitochondrial aggregation occurs due to abnormal transport of mitochondria [46,104]. Furthermore, previous studies indicate that upregulation of neuroglobin is able to resolve the condensation of actin microtubules following induction by H₂O₂, suggesting neuroglobin has a key role in maintaining the integrity of the cell membrane [47]. Since the transient migration of mitochondria throughout the cytosol in neurons rely on actin microtubules, neuroglobin might play an indirect function in promoting this process [105]. Despite the literature on the role of neuroglobin in mitochondria migration, more studies should be carried out to assess the mechanisms underlying neuroglobin function in modulating the mitochondrial dynamics and its involvement in the etiopathogenesis of neurodegenerative disorders.

1.6. Neuroglobin-mitochondria crosstalk at molecular level

There are numerous proteins and molecules inside mitochondria that originate from cytosol and are transported into mitochondria when a neuroinflammatory stimulation occurs. Amongst these proteins, bcl-2 family members are the most important apoptosis-related molecules that respond to cell death signals [59]. Other than exogenous apoptosis-related molecules, mitochondria also harbor an number of endogenous molecules related to apoptosis, such as neuroglobin, that play a role in supporting and protecting neuronal cells [29]. Other than mediating apoptosis signaling, ROS production and ATP production, neuroglobin has been indicated to interact with other molecules, such as ubiquitin C, Na/K ATPase beta 1, voltage dependent anion channel (VDAC), and Cyc 1 [54]. Among the neuroglobin-binding molecules, Cyc 1 and VDAC have been shown to play an important role in maintaining the survival and protection of neurons. Cyc 1 is associated with pathological conditions and has been implicated in oxidative stress and modulation of hypoxia inducible factor-1 alpha (HIF-1α) when hypoxic conditions occur [106]. Additionally, VDAC has a key role in mediating the opening of mitochondrial PTP [107], leading to the release of Cyt c into the cytoplasm [68] and initiation of apoptosis pathways. On the other side, neuroglobin reduces the release of Cyt c by preventing the opening of mitochondrial PTP opening [70]. OGD/reoxygenation was indicated to mediate the localization of neuroglobin in mitochondria [29]. However, the detailed function of neuroglobin in mitochondria and its binding with mitochondrial proteins requires further investigation.

2. Conclusions

 Neuroglobin is an endogenous neuroprotective protein that plays a role in several neurodegenerative conditions (Fig. 2). Mitochondria play a vital role in mediating apoptosis or neuronal survival in multiple neurodegenerative disorders. They do this by modulating several physiological cellular processes, including oxidative stress, energy metabolism and apoptosis signaling. Neuroglobin has an active role in protecting the cell against oxidative stress by degrading ROS, maintaining ATP sources and modulating apoptosis. Moreover, neuroglobin organizes the movement of mitochondria inside cell for important physiological requirements. The modulation of the mitochondrial dynamics by neuroglobin might opens up novel avenues in the field of...
neuroglobin and neurodegenerative diseases. Recent approaches, like nanoparticles, to deliver neuroglobin to the brain might be promising in the treatment of neurological diseases [108,109]. Nonetheless, the precise interactions among neuroglobin and proteins with biological function in mitochondria have not been fully explored. Experimental models using neuroglobin suggest that neuroglobin is a valuable tool in the treatment of neurodegenerative diseases; however, further investigations are required to confirm the exact mechanisms of action of this globin [110]. When a complete picture of how neuroglobin functions is available, one can target this signaling pathway to design therapeutics which enhance the beneficial effects of neuroglobin in neurodegenerative disorders.

Disclosure of conflict of interest

None.

Declaration of competing interest

None.

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