Association of Mitochondrial Signaling in Alzheimer's Disease and Hypoxia

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CHAPTER 5

Association of Mitochondrial Signaling in Alzheimer's Disease and Hypoxia

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Abstract: Neurodegenerative diseases, particularly those associated with aging such as Alzheimer's disease, represent a significant public health concern. The development of effective treatments is, however, hindered by the complex, multigenic nature of these diseases and by their poorly understood molecular pathophysiology. Mitochondria seem to play a primary role in neurodegeneration, due to the high energy demand of the brain. These organelles are the main producers of energy through the tricarboxylic acid cycle and host a high number of biochemical pathways including those involved in storage and maintenance of intracellular calcium levels, cellular homeostasis and survival pathways. However, mitochondria are a double edge sword. In the presence of certain oxidative stimuli, for instance, when oxygen demand exceeds supply (hypoxia), mitochondria can activate several death pathways. Indeed, hypoxia has been implicated in several neurodegenerative diseases including Alzheimer's disease**.** Current knowledge supports the idea that during hypoxic events mitochondrial complex III produces high levels of reactive oxygen species (ROS), which play a key role in the regulation of the transcription factor hypoxia inducible factor 1 that triggers several death effectors. In this chapter we will discuss the involvement of mitochondria in AD putting focus on the mitochondrial pathways activated by hypoxia, which could eventually lead neurodegenerative events.

Keywords: Alzheimer's disease; mitochondrial dysfunction; reactive oxygen species; cerebral amyloid angiopathy; β-secretase; Aβ neurotoxicity

INTRODUCTION

Diseases resulting from degenerative changes in the nervous system markedly impact the lives of millions and pose growing public health challenges. Alzheimer's disease (AD), the most common form of dementia, is affecting an increasing number of individuals each year with the number of patients reaching upwards 26.6 million people worldwide in 2006, a number that could quadruple by 2050 [1,2]. Therefore, the prevention and treatment of AD represents one of the critical goals of medical research.

AD is the most common cause of dementia among older people. This degenerative brain disease typically begins with a subtle decline in memory and progresses to global deterioration in cognitive and adaptive functioning. The neuropathological features associated with the disease include the presence of extracellular senile plaques, intracellular neurofibrillary tangles (NFT), and the loss of basal forebrain cholinergic neurons that innervate the hippocampus and the cortex. NFT are formed from paired helical filaments composed of neurofilaments and hyperphosphorylated tau protein. Senile plaques are formed mostly from the deposition of the amyloid-β (Aβ) peptide, a 39–43 amino acid peptide generated through the proteolytic cleavage of the amyloid-β precursor protein (AβPP) by the β- and γ-secretases [3,4]. Aβ deposits may also be found in brain parenchyma and in the walls of small brain arteries, leading to cerebral amyloid angiopathy (CAA). CAA is associated with local loss of neurons, synaptic abnormalities, microglial activation and microhaemorrhage. Such alterations will impact neuronal and synaptic function and, even at its earliest stage, Aβ deposits around brain vessels could certainly interfere with the dynamic adaptation of cerebral blood flow (CBF) to changing brain function.

Accumulating evidence shows that vascular changes play an important role in AD pathogenesis [5,6]. It has been

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shown that atherosclerosis, stroke and cardiac disease may cause cerebrovascular dysfunction and trigger AD pathology [7]. Magnetic resonance imaging (MRI), transcranial doppler measurements, and single photon excitation computed tomography (SPECT) in humans showed that the resting CBF is significantly reduced and is an early event in AD. Arterial spin-labeling MRI has demonstrated cerebral hypoperfusion in AD patients [8]. A previous study performed with functional MRI (fMRI) that use blood oxygenation level dependent (BOLD) contrast to measure increases in CBF during a task that assesses episodic memory have established that there is a delay in the CBF response in patients with mild cognitive impairment (MCI), this delay being more pronounced in AD patients [9]. As MCI may represent a prodromal state for AD, these results suggest that CBF reductions are present in the early stages of AD pathophysiology.

A reduction in blood flux leads to hypoxia (a decrease in oxygen levels) in brain tissue [10]. Hypoxia alters the synaptic plasticity and promotes mitochondrial dysfunction, oxidative stress, and apoptosis in several regions of the brain including the cerebral cortex, hippocampus and striatum [11-15]. It has also been shown that disruption of calcium homeostasis, following hypoxia, may contribute to the neurotoxicity of Aβ and subsequent development of AD [16]. Sun and colleagues [17] reported that hypoxia leads to increased β-secretase activity and production of Aβ. Similarly, Guglielmotto and collaborators [18] demonstrated that hypoxia up-regulates β-secretase potentiating the production of Aβ. The authors reported that this effect is mediated by mitochondrial reactive oxygen species (ROS) [18]. In this chapter, we will give an overview about the role of mitochondria in physiologic and neuropathologic conditions, particularly in AD. The hypoxia-mediated mitochondrial pathways, particularly that involving the hypoxia inducible factor 1α (HIF-1α), will also be discussed.

MITOCHONDRIA AND THE BRAIN

The brain has a high energy demand, and although it represents only 2% of the body weight, it receives 15% of cardiac output and accounts for 20% of total body oxygen consumption [4,19]. Physiological demand for oxygen can also vary depending on brain tissue requirements at a given moment [20]. Brain average oxygen consumption is, with exception of myocardial tissue, higher than oxygen consumption in other body tissues and averages approximately 3,5ml/100g/min [21]. As such, complex cellular oxygen sensing systems have evolved for tight regulation of oxygen homeostasis and avoid or, at least, minimize brain damage [22].

Glucose, the major fuel in the brain, is transported across the cell membranes by facilitated diffusion mediated by glucose transporter proteins. More than any other organ, the brain is entirely dependent on a continuous supply of glucose from the circulation since glucose is almost the sole substrate for energy metabolism [23]. This extraordinary energy requirement is largely driven by energy needed to maintain ion gradients across the neuronal plasma membrane that is critical for the the generation of action potentials. This intense energy requirement is continuous and even brief periods of oxygen or glucose deprivation can result in neuronal dysfunction or death [24]. Despite its high energy demand to maintain "housekeeping" functions, the brain cannot store energy very well. Cerebral energy only sustains brain function for a few minutes before irreversible injury, which result from metabolic failure [25].

Mitochondria are ubiquitous and dynamic organelles responsible for many crucial cellular processes in eukaryotic organisms. In fact, mitochondria are considered the "gatekeepers of life and death". These organelles play a key role in cellular energy production [26-29]. The metabolism of glucose through the tricarboxylic acid (TCA) cycle generates the electron donors NADH and succinate that donate electrons to complexes I and II of the respiratory chain, respectively. Electrons from these complexes are transferred to coenzyme Q, Complex III, cytochrome c, complex IV and finally to molecular oxygen that is reduced to water. The electron transport system is organized in this way in order to regulate ATP production (Fig. **1**). Indeed, part of the energy of those electrons is used to pump protons to the mitochondrial matrix. These protons (voltage gradient) are then used by ATP synthase to generate ATP from ADP (Fig. **1**). The ATP generated during this cycle is utilized to provide the energy necessary to carry out active cellular processes.

Although these intracellular organelles are mainly devoted to energy production they are also an important source of reactive oxygen species (ROS) [30-33]. The oxidative phosphorylation system (OXPHOS) is not 100% efficient and approx. 20% of protons undergo regulated proton leak leading to the generation of ROS and, possibly, thermogenic processes [34-37]. Thus a basal production of ROS occurs when OXPHOS is uncoupled from ATP synthesis [20].

Indeed, ROS and reactive nitrogen species (RNS) are products of normal cellular metabolism [38, 39]. These reactive species may play a dual role, deleterius or beneficial depending on their levels (Fig. **2**) [40].

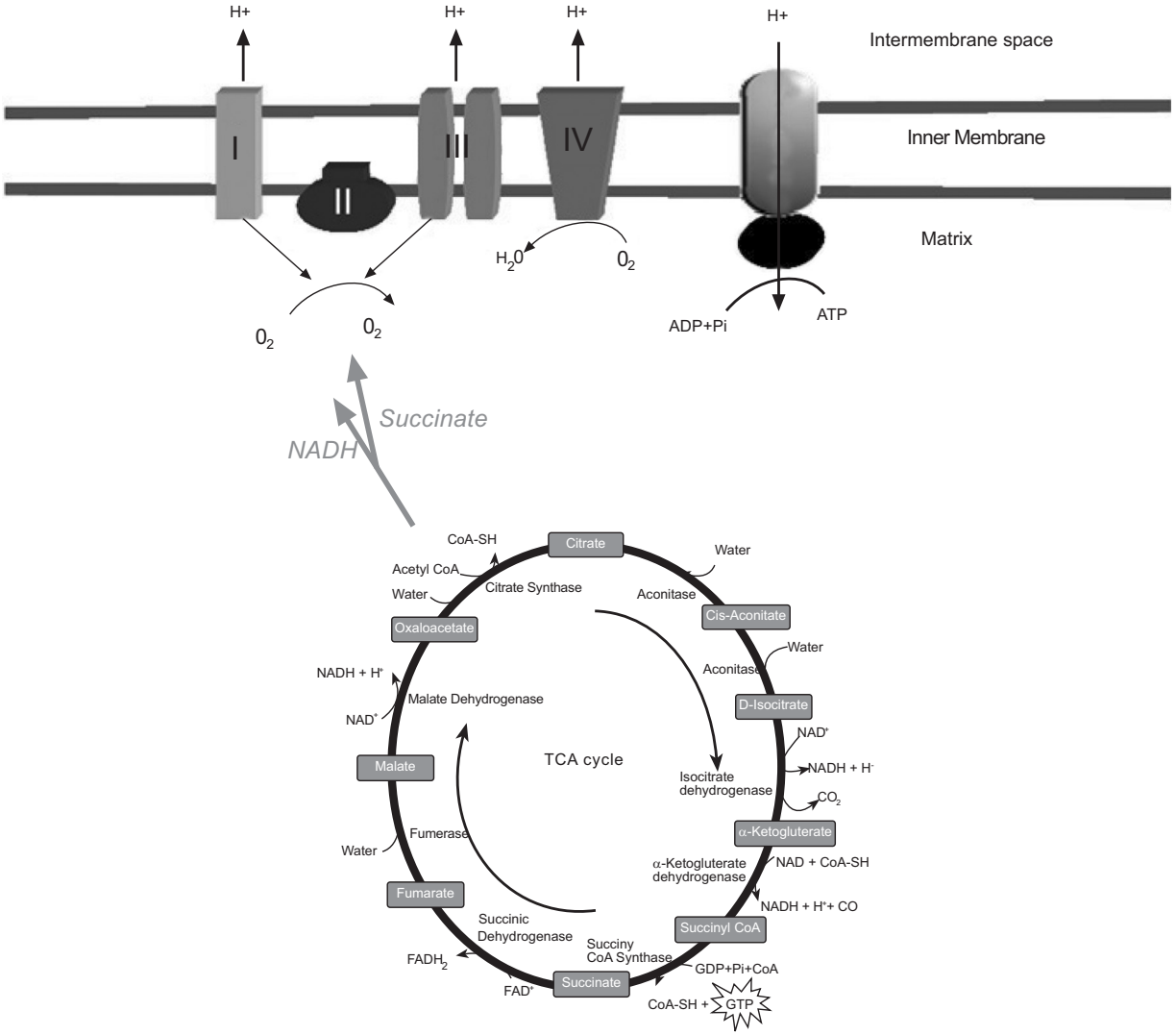

Figure 1: Mitochondria and energy production. The primary physiological function of mitochondria is to generate adenosine triphosphate (ATP), through oxidative phosphorylation via the electron transport chain. Glucose enters in tricarboxylic acid (TCA) cycle where NADH and succinate are produced in order to provide electrons to the complex I and II, respectively, of the respiratory chain. Electrons from these complexes are transferred through the respiratory chain, with concomitant basal production of reactive oxygen species namely superoxide ($O_2^{\bullet-}$) and, finally transferred to molecular oxygen that is reduced to water. Part of the energy of these electrons is used to pump protons to the mitochondrial matrix creating a voltage gradient used by ATP synthase to generate ATP from ADP.

Low or moderate levels of reactive species are involved in physiological processes like the expression of several genes involved in antioxidant defence and survival and regulation pathways (Fig. **2**) [41]. It was also shown that most cell types elicit a small oxidative burst that generates low levels of ROS when they are stimulated by cytokines, growth factors and hormones [42]. This led to the assumption that the initiation and/or proper functioning of several signal transduction pathways rely on the action of reactive species as signalling molecules which may act on different levels in the signal transduction cascade. Reactive species can thus play a very important physiological role as secondary messengers [43-47].

However, high levels of reactive species promote oxidative imbalance and activate anomalous signaling mechanisms related to various disease states [48,49]. The term ‘‘oxidative stress” describes the adverse interactions of mo-

lecular oxygen (O_2), or its reactive derivatives, with biomolecules causing a disequilibrium between the generation of cellular damaging molecules and the cellular capacity for detoxification [39]. During aging and pathological conditions, the production of reactive species exceeds the scavenging capacity of endogenous systems, resulting in the damage of cellular components such as proteins, lipids, and nucleic acids. Besides being one major source of ROS, mitochondria are also one of the preferential targets of reactive species. The mitochondrial DNA (mtDNA) is particularly susceptible to oxidative damage due to its lack of protective histones, limited repair capabilities, and proximity to the electron transport chain [50-53]. Oxidative damage of mitochondrial biomolecules causes the impairment of these organelles, which potentiates the release of certain apoptogenic factors that may activate the intrinsic death pathway (Fig. **2**) [54].

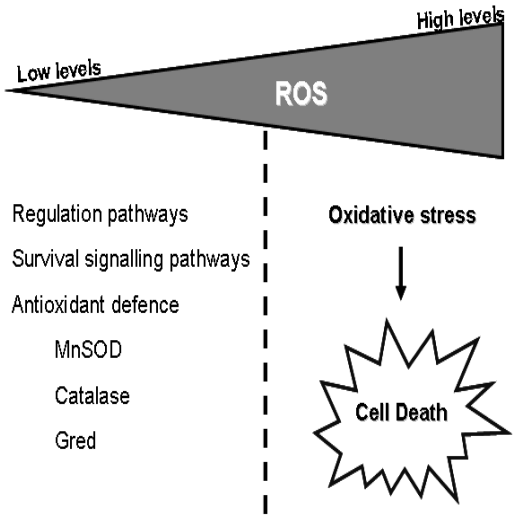

Figure 2: Dual role of mitochondrial reactive oxygen species. The continuous electron leak from the respiratory chain leads to the generation of damaging reactive oxygen species (ROS) that play a dual role. Low levels of ROS induce the expression of several genes involved in antioxidant defence including manganese superoxide dismutase (MnSOD), catalase, glutathione reductase (Gred), and intracellular signalling and regulation. However, high levels of ROS promote oxidative stress and activate anomalous signalling mechanisms that will ultimately lead to cell death.

MITOCHONDRIAL DYSFUNCTION IS A KEY EVENT IN NEURODEGENERATION

Considerable data support the hypothesis that mitochondrial abnormalities link gene defects and/or environmental insults to neurodegeneration [55]. It is now well known that subtle alterations in energy metabolism can lead to insidious pathological changes in neuronal cells [56-58]. Indeed, the literature shows that reduced glucose utilization and energy metabolism and oxidative stress are key players involved in the onset and progression of AD [4,59-63], oxidative stress occurring prior to cytopathology [64,65]. Studies performed in postmortem AD brain and fibroblasts show a reduction in the activity of pyruvate dehydrogenase, isocitrate dehydrogenase and α-ketoglutarate dehydrogenase, three TCA complexes [66,67]. A reduction in the activity of the mitochondrial complexes I, III and IV have also been found in platelets and lymphocytes from AD patients and postmortem brain tissue [68-71]. Several *in vitro* studies corroborate the idea that mitochondria are key players in AD. It has been previously shown that Aβ requires functional mitochondria to induce toxicity [72]. Furthermore, Hansson *et al.* [73] identified an active γ-secretase complex in rat brain mitochondria. Being composed by nicastrin (NCT), anterior pharynx-defective-1 (APH-1), and presenilin enhancer protein 2 (PEN2), this γ-secretase complex cleaves, among other substrates, amyloid β protein precursor (AβPP) generating Aβ and AβPP-intracellular domain. Furthermore, the presence of AβPP was detected in mitochondrial membranes of PC12 cells bearing the Swedish double mutation in AβPP gene [74]. It was also shown that Aβ potentiates the opening of the mitochondrial permeability transition pore (PTP) induced by Ca^{2+} [75,76]. The PTP is a non-selective, high-conductance channel that spans the inner and outer mitochondrial membranes [77-79] and is modulated by several physiological factors [80,81]. The sudden increase in the permeability of the inner mitochondrial membrane plays a key role in apoptotic cell death by facilitating the release of apoptogenic factors such as cytochrome c that will activate the apoptotic cell death pathway (Fig. **3**). Du and collaborators [82] reported that interaction of cyclophilin D, an an integral part of the PTP, with with mitochondrial Aβ potentiates mitochon-

drial, neuronal and synaptic stress. It was also observed that cyclophilin D deficiency substantially improves learning and memory and synaptic function in an AD mouse model and alleviates Aβ-mediated reduction of long-term potentiation [82].

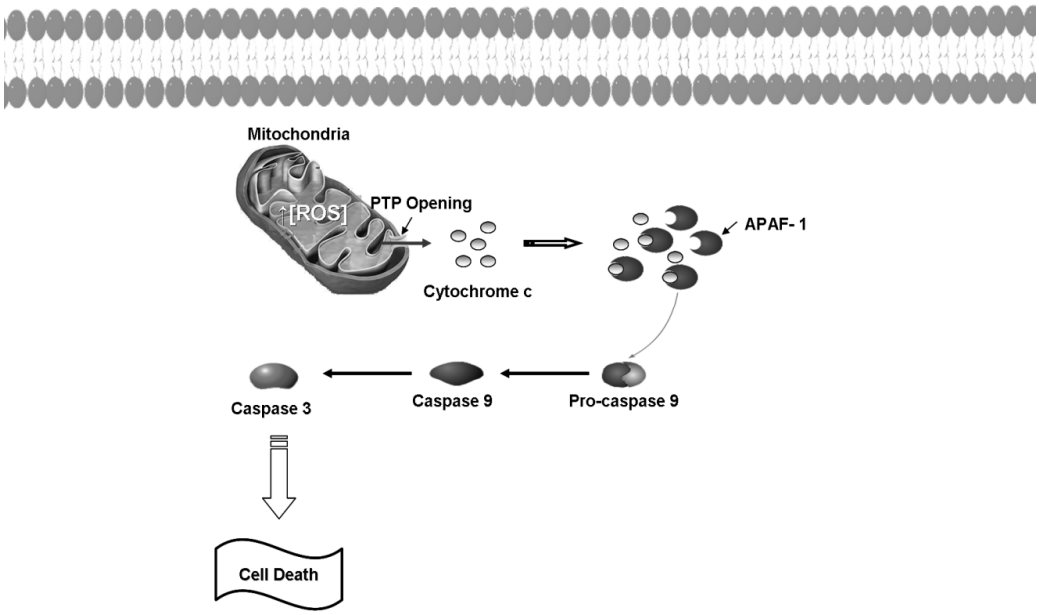

Figure 3: Mitochondrial-mediated cell death. The impairment of mitochondria is intimately associated with an increase in reactive oxygen species (ROS) levels, a decrease in ATP levels and calcium (Ca^{2+}) dyshomeostasis. One important phenomenon associated with mitochondrial dysfunction and oxidative stress is the induction of the permeability transition pore (PTP). The sudden increase in the permeability of the inner mitochondrial membrane plays a key role in apoptotic cell death by facilitating the release of apoptogenic factors such as cytochrome c. Once released to the cytosol, cytochrome c interacts with apoptotic protease activating factor-1 (APAF-1) which cleaves pro-caspase 9 into an active form, caspase-9, that in turn activates caspase-3, resulting in the activation of apoptotic cell death pathway.

The neurodegenerative processes occurring in AD are intimately associated with the apoptotic pathway. Previous studies performed in AD brains found an imbalance between pro-apoptotic (Bax, Bak and Bad) and anti-apoptotic (Bcl-2 and Bcl-x_L) proteins [83,84] and the initiator caspases 8 and 9 and the effector caspases 3 and 6 [85-88]. Other studies demonstrated a marked decrease in the expression of some anti-apoptotic gene such as NCKAP1 [89]. It was also show the existence of active caspases and caspase-cleaved substrates in neurons, around senile plaques and NFT [84,90,91], and also in postsynaptic densities [92]. Both caspase-cleaved AβPP and activated caspase 3 have been shown to be present and associated to granulovacuolar degeneration, a diagnostic AD neuropathological sign in brains of affected patients [93]. Furthermore, a marked co-localization of pathological hyperphosphorylated tau, cleaved caspase-3 and caspase-6 have been recently reported in TUNEL-positive neurons in the brainstem of AD patients [94]. These studies show that in AD a close association between mitochondrial dysfunction, oxidative stress and apoptotic cell death occurs.

IS THE HYPOXIA-INDUCED MITOCHONDRIAL IMPAIRMENT A CAUSE OF AD?

Cerebrovascular insufficiency such as reduced blood supply to the brain or disrupted microvascular integrity in cortical regions may play a key role in the chain of events ending in cognitive failure. Endothelial cells from small vessels are characterized by a relatively high number of mitochondria that can produce the energy necessary for the functioning of specific blood brain barrier (BBB) transport proteins [95].

The aged and degenerative brain is characterized by a decreased CBF, lower metabolic rates of glucose and oxygen and a compromised structural integrity of the cerebral vasculature particularly that of the microvessels (Fig. **4**). It has been shown a profound involvement of endothelial dysfunction in AD-related cerebral hypoperfusion and AD

pathophysiology [96]. Furthermore, Aβ deposition in brain vessels occurs in many AD patients and results in CAA and decreased blood fluxes in the brain **(Fig.4)** [4,97]. Data from the literature showed that application of exogenous Aβ to normal blood vessels *ex vivo* causes endothelium-dependent vasoconstriction with decrease in blood fluxes and, consequently, oxygen levels [98,99].

Cells utilize oxygen as the final electron acceptor in the aerobic metabolism of glucose to generate ATP which fuels most active cellular processes. The occurrence of hypoxia leads rapidly to metabolic crisis and represents a severe threat to ongoing physiological function and, ultimately, viability [20]. Hypoxia has been implicated in several brain pathologies including stroke, head trauma, neoplasia and neurodegenerative disease [22, 100,101].

The pathways underlying hypoxic neurotoxicity and cell death are complex and multifaceted and involve several cellular responses, including oxidative stress, altered ionic homeostasis, mitochondrial dysfunction and activation of apoptotic cascades [12,1-2,103]. It has been shown that neuronal apoptosis associated with hypoxic/ischemic injury, aging, and neurodegenerative diseases is due to calcium overload resulting from the mobilization of extracellular calcium through *N*-methyl D-aspartate (NMDA) receptors [104-107]. Hypoxia also triggers free radical generation and depletion of antioxidant status, thus leading to oxidative damage [108,109]. Changes in synaptic efficacy occur very early during hypoxia and may indeed, be the first response of the neuron to ischemic insult [110,111].

Studies have suggested that hypoxia can induce apoptosis dependent on transcriptional activation of apoptotic factors [112]. HIF-1 is a heterodimeric protein composed of a constitutively expressed HIF-1β subunit and an inducible HIF-1α subunit. Under normoxic conditions, HIF-1α is hydroxylated by prolyl hydroxylase enzymes (PHDs) and rapidly degraded by the ubiquitin-proteasome system. On the other hand, during hypoxic conditions, enzymatic inhibition of PHDs abrogates HIF-1α proteasomal degradation and results in HIF-1α stabilization and translocation to the nucleus (Fig. **4**). In the nucleus, HIF-1α recruits HIF-1β and modulates the expression of a wide range of genes involved in angiogenesis, metabolism, apoptosis, and cell survival [113,114].

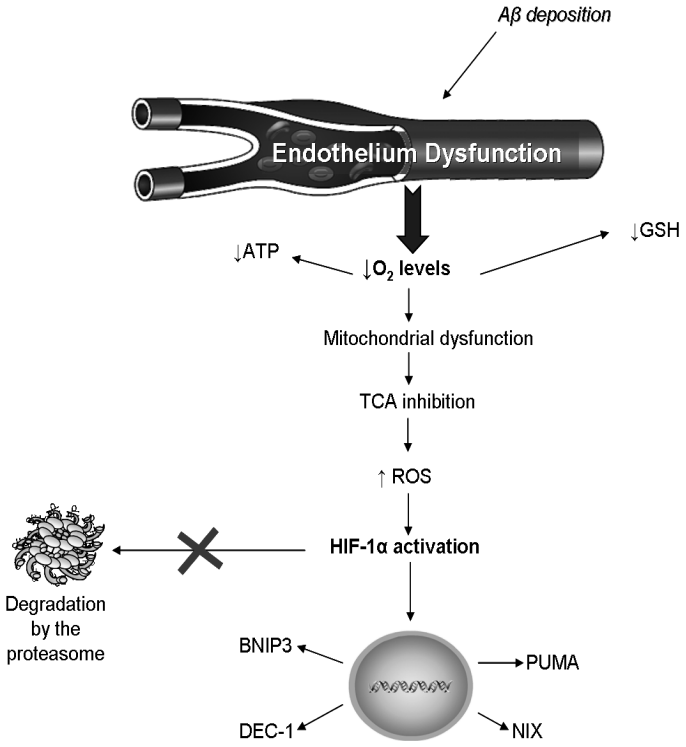

Figure 4: Hypoxia-mediated cell death in neurodegeneration. Hypoxia has been implicated in several pathologies of the central nervous system. In Alzheimer's disease the deposition of the amyloid β (Aβ) protein in brain vessels potentiate the occurrence of hypoxic phenomena. A drop in tissue oxygen levels to the point where oxygen demand exceeds supply rapidly leads to a metabolic crisis putting in danger the ongoing physiological functions. This metabolic crisis comprises a severe energy (ATP) drop that results from an impairment of mitochondria function, including the inhibition of the tricarboxylic acid (TCA) cycle. These

alterations are intimately associated with an increase in the production of reactive oxygen species (ROS) as well as reactive nitrogen species, namely nitric oxide (NO) and a concomitant decrease in antioxidants namely reduced glutathione (GSH), the first line of defense against oxidative stress. Hypoxia-inducible factor-1 (HIF-1 α) is a transcription factor that is oxygen sensitive. In physiological conditions HIF-1α is continuously degraded by proteasome. However, in the presence of low levels of oxygen (O_2) and increased levels of ROS, HIF-1α is activated and translocated to the nucleus where it will bind to hypoxia response elements (HREs) increasing the expression of pro-apoptotic proteins, namely the defective chorion-1 (DEC-1), Bcl2/adenovirus E1B 19kD-interacting protein-3 (BNIP3), its orthologue Nip3-like protein X (NIX), PUMA and cyclin G2 leading to cell death. See text for more complete information

Previous studies demonstrated that under hypoxic conditions mitochondrial ROS, produced at complex III, are necessary and sufficient to stabilize HIF-1α avoiding its degradation by the proteasome (Fig. **4**) [115-117]. Other studies, however, reported a general decrease in ROS levels under hypoxic conditions [118] and showed that a functional respiratory chain may not be necessary for HIF-1α regulation [22,119,120]. More recently, Serra-Pérez and collaborators [121] reported that postischemic metabolic alterations in TCA metabolites impair HIF-1 α degradation in the presence of oxygen by decreasing its hydroxylation, and highlight the involvement of metabolic pathways in HIF-1α regulation besides the well known effects of oxygen.

Whether and to what extent the HIF system may participate in the disease process remains to be elucidated. Indeed, the literature supports a dual role of the HIF system, depending on whether it is the cause or the consequence [22]. Previous studies reported that initially HIF activates a survival pathway that involves the expression of angiogenic and vasodilators genes such as vascular endothelial growth factor (VEGF), inducible nitric oxide synthase and erythropoietin [122-126]. However, sustained and prolonged activation of the HIF pathway may lead to a transition from neuroprotective to cell death responses. The long-lasting activation includes responses with adverse effects on cell function by inducing cell-cycle-arrest-specific and pro-apoptotic proteins such as defective chorion-1 (DEC-1), Bcl2/adenovirus E1B 19kD-interacting protein-3 (BNIP3), its orthologue Nip3-like protein X (NIX), PUMA and cyclin G2 expression (Fig. **4**). In addition, direct stabilization through the pro-apoptotic protein p53 has been suggested by studies demonstrating physical and functional interactions between HIF-1α and p53 (Fig. **4**) [127]. The protein p53 is a master regulator of cell death by inducing apoptosis through the control of apoptosis-related gene expression [128]. In response to certain death stimuli, a fraction of stabilized p53 rapidly translocates to mitochondria launching a rapid pro-apoptotic response in a transcription-independent manner that jump-starts and amplifies the slower transcription dependent response [129-131].

Several studies have been conducted to establish the role of hypoxia in neurodegeneration and, specifically, in AD. It has been previously shown that cerebral hypoxia results in increased activity of caspase-9 and caspase-3 in the cerebral cortex of newborn piglets [132,133]. The mechanism of activation of caspase-9 during hypoxia that leads to initiation of programmed cell death in mammalian brain tissue is not known, but data indicate that the decrease in ATP levels and cytochrome c release had primary roles in this process (Fig. **4**) [134]. Also the increase in nitric oxide levels induced by hypoxia has been shown to activate caspase-9 through a transcription-dependent mechanism. Indeed, there is a nitric oxide-mediated increase in pro-apoptotic proteins such as Bax and Bad during hypoxia that may lead to APAF-1 activation resulting in the conversion of procaspase-9 into active caspase-9 and subsequent activation of caspase-3. It has been also reported that hypoxic stress induces a down-regulation of anti-apoptotic proteins of the Bcl-2 family promoting the apoptotic cell death [135]. Additionally, expression of HIF-1-regulated "pro-death" BH3-only family members, such as BNIP3, has also been shown to increase following cerebral ischemia [136-139]. Recently, Chen and collaborators [140] reported that the silencing of HIF-1α inhibits the expression of VEGF and apoptotic-related proteins such as p53 and caspase-3 protecting neurons against ischemia-reperfusion.

The inhibition of TCA cycle and depletion in glutathione (GSH) levels as a result of its greater use for quenching the accelerated free radical generation accompanied by a concomitant increase in glutathione disulfide was also observed in hippocampal cells under hypoxia (Fig. **4**) [141]. Recently, Sarada *et al.* [142] reported that neuroblastoma cells exposed to hypoxia present increased free radical production and apoptosis and decreased GSH content and glutathione reductase, glutathione peroxidase and superoxide dismutase activities.

Wang and collaborators [143] demonstrated that the expression of APH-1A, a component of the γ-secretase complex, and the γ-secretase mediated Aβ and Notch intracellular domain generation are regulated by HIF-1. Another study showed a functional hypoxia-responsive element in the β-site AβPP cleavage enzyme 1 (BACE1) gene pro-

moter [17]. The authors report that hypoxia up-regulated γ-secretase cleavage of AβPP and Aβ production by increasing BACE1 gene transcription and expression both *in vitro* and in vivo. Hypoxia treatment markedly increased Aβ deposition and neuritic plaque formation and potentiated the memory deficit in Swedish mutant AβPP transgenic mice [17]. These results clearly demonstrate that hypoxia can facilitate AD pathogenesis, and they provide a molecular mechanism linking vascular factors to AD. Zhang and collaborators [144] also showed that acute hypoxia increases the expression and the enzymatic activity of BACE1 by up-regulating the level of BACE1 mRNA, resulting in increases in the AβPP C-terminal fragment-β and Aβ Guglielmotto and collaborators [18] observed that hypoxia significantly increased BACE1 gene transcription through an early up-regulation dependent on the release of mitochondrial ROS and a late up-regulation due to the overexpression and activation of HIF-1α, resulting in increased BACE1 activity and Aβ production. Furthermore, the authors reported that the oxidative stress-mediated up-regulation of BACE1 is mediated by c-jun N terminal kinase pathway [18]. This study strengthens the hypothesis that oxidative stress is a basic common mechanism of Aβ accumulation. A recent study demonstrated that salidroside is able to attenuate abnormal processing of AβPP induced by hypoxia in SH-SY5Y cells, providing a new insight into prevention and treatment of AD [145]. Furthermore, Fang and collaborators [146] reported that hypoxia promotes the phosphorylation of tau protein via ERK pathway suggesting that hypoxia may potentiate NFT formation.

CONCLUDING REMARKS

Mitochondrial ROS have a dual role since at high levels they potentiate cell death pathways and at low/moderate levels they activate survival pathways. At low levels of oxygen cells are unable to generate sufficient energy for survival so, a mechanism for sensing a decrease in the oxygen level before it reaches a critical point is crucial for cells survival. Under low levels of oxygen levels, HIF-1 is activated leading to adaptations to the hypoxic environment. It has been shown that under hypoxic conditions, mitochondrial ROS are required for HIF-1 activation. Although the exact mechanism remains unclear, it seems that HIF system activates several pathways that cover a wide array of responses to hypoxia, ranging from mechanisms that increase cell survival to those inducing cell cycle arrest or even apoptosis. Recent studies show that hypoxia potentiates the development of AD since it favours Aβ production and tau phosphorylation. Although AD is intimately associated with mitochondrial dysfunction, oxidative stress and hypoxic episodes, the role of HIF is this pathology remains largely unknown. More studies should be done to clarify the molecular mechanisms that regulate HIF-1 in order to evaluate the value of this transcription factor as a therapeutic target in neurodegenerative diseases associated to hypoxia such as AD.

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