Brain mitochondrial dysfunction as a link between Alzheimer’s disease and diabetes

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Available online 20 February 2007

Abstract

It has been argued that in late-onset Alzheimer’s disease a disturbance in the control of neuronal glucose metabolism consequent to impaired insulin signalling strongly resembles the pathophysiology of type 2 diabetes in non-neural tissue. The fact that mitochondria are the major generators and direct targets of reactive oxygen species led several investigators to foster the idea that oxidative stress and damage in mitochondria are contributory factors to several disorders including Alzheimer’s disease and diabetes. Since brain possesses high energetic requirements, any decline in brain mitochondria electron chain could have a severe impact on brain function and particularly on the etiology of neurodegenerative diseases. This review is primarily focused in the discussion of brain mitochondrial dysfunction as a link between diabetes and Alzheimer’s disease.

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Keywords: Alzheimer’s disease; Antioxidants; Brain; Diabetes; Insulin; Mitochondria; Neurodegeneration; Oxidative stress

1. Introduction

Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by a selective neuronal cell death associated with two hallmark pathological lesions: the intracellular neurofibrillary tangles (NFTs) and extracellular amyloid deposits in the form of senile plaques. The etiological events leading to AD pathogenesis are unclear. Although age and the inheritance of predisposing genetic factors appear to play a major role, more recent evidence suggests that the development and progression of AD is subject to a wide variety of both environmental and genetic modifiers [1,2]. There is no single gene that accounts for AD heritability, despite some clues that have been provided by genetic analysis of the rare cases of early-onset familial AD which are caused by missense mutations in the amyloid β precursor protein (AβPP) and presenilin-1 and -2 genes. The vast majority of late-onset AD cases are sporadic in origin. Mutations and polymorphisms in multiple genes are likely to contribute to sporadic AD pathogenesis together with non-genetic factors. The specific accumulation of neurotoxic amyloid-β (Aβ) [3] derived from the post translational proteolysis of AβPP [4] in the central nervous system (CNS) appears to represent a major pathological step in the evolution of AD [5]. AD has been thought to occur due to the accumulation of aggregated neurotoxic Aβ appearing in specific brain regions (hippocampus and cerebral cortex), triggering an inflammatory response, neuronal cell death and gradual cognitive decline [5].

Diabetes mellitus is a heterogeneous metabolic disorder characterized by hyperglycemia. In type 1 diabetes, which generally develops at a young age, the principal defect is an auto-immune-mediated destruction of pancreatic cells, leading to insulin deficiency. In type 2 diabetes the principal defect is insulin resistance, leading to a relative insulin deficiency. The islet of Langerhans in type 2 diabetes is characterized by β-cell loss [6,7] and islet amyloid derived from islet amyloid polypeptide (IAPP) [8–10], a protein coexpressed and secreted with insulin by β-cells. Similarly...
to Aβ peptide, IAPP spontaneously forms into amyloid aggregates in an aqueous environment [11]. Furthermore, it has been reported that degeneration of pancreatic islets is also associated with NFTs formation (for review see [12]). Similarly to AD, the incidence of type 2 diabetes strongly increases with age. Altogether these findings implicate a close biological relationship between type 2 diabetes and AD.

In addition to complications that affect the eyes, kidneys, heart, blood vessels and nerves, diabetes mellitus is associated with damage to the CNS and cognitive deficits [13,14]. Impairment of learning and memory has been documented in both type 1 and type 2 diabetes. CNS deficits range from moderate to severe, depending on the quality of glycemic control, and involve mainly verbal memory and complex information processing [15–17].

Furthermore, it has been shown that insulin affects several brain functions including cognition and memory; and several studies have established links between insulin resistance, diabetes mellitus and AD [18]. Recent evidence indicates that insulin regulates the metabolism of Aβ and tau proteins [19–21]. Hoyer [22] was the first to suggest that desensitization of the neuronal insulin receptors and signalling events in AD, leads to a reduction in acetylcholine and a corresponding decrease in cerebral blood flow. These abnormalities result in chronic and increasing deficits in brain oxidative metabolism.

Due to the increasing number of data demonstrating a connection between diabetes and AD, efforts have been developed to elucidate the exact mechanism(s) underlying this connection. Although both disorders possess several overlapping features, mitochondrial dysfunction is one of the most relevant rendering mitochondrion an important target of scientific research. This review starts by given an overview about the involvement of insulin signal transduction in AD pathophysiology followed by the discussion of glucose/energetic metabolism deficiency in this disease. The last part of this review culminates with the discussion of mitochondrial dysfunction as a link between diabetes and AD.

2. Insulin and Alzheimer’s disease pathophysiology

Abnormalities in insulin metabolism, pertinent to type 2 diabetes, are among the central factors thought to mechanistically influence the onset of AD via their influence on synthesis and degradation of Aβ. For example, there is evidence indicating that insulin itself may significantly promote extracellular amyloidogenic Aβ peptides through mechanisms that involve the acceleration of AβPP/Aβ trafficking from the trans-Golgi network, a major cellular site for Aβ generation, to the plasma membrane [21]. Additionally, recent studies have indicated that certain signal transduction pathways downstream of the insulin receptor, may also promote the generation of Aβ peptides by modulating the cleavage of the parent AβPP at the γ-secretase site [23], a site determinant of Aβ amyloidogenicity. Although this evidence tentatively suggests that type 2 diabetes might play an important role in AD through mechanisms that involve Aβ peptide generation, alternate studies suggest that insulin may also provoke amyloid accumulation by limiting Aβ degradation via direct competition for the insulin-degrading enzyme (IDE). IDE is a zinc-metalloproteinase that preferentially cleaves proteins with a propensity to form β-pleated sheet-rich amyloid fibrils [24,25], such as Aβ peptides [26,27]. This relationship of IDE with Aβ is supported by recent evidence indicating that IDE activity in the brain is negatively correlated with Aβ content [26,27], and that IDE expression is decreased in the AD brain [28,29].

Furthermore, it has been reported that Aβ40 and Aβ42 reduce insulin binding and insulin receptor autophosphorylation. The reduction in binding seems to be caused by a decrease in the affinity of insulin to the insulin receptor, which suggests that Aβ is a direct competitive inhibitor of insulin binding and action [30].

Recently, Steen and collaborators [31] demonstrated the existence of extensive abnormalities in insulin and insulin-like growth factor type I and II (IGF-I and IGF-II) signalling mechanisms in AD brains. These abnormalities were associated with reduced levels of insulin receptor substrate (IRS) mRNA, tau mRNA, IRS-associated phosphotidylinositol 3-kinase, and phospho-Akt (activated), and increased glycogen synthase kinase-3β activity and AβPP mRNA expression. The strikingly reduced CNS expression of genes encoding insulin, IGF-I, and IGF-II, as well as the insulin and IGF-I receptors, led the authors to suggest that AD may represent a neuro-endocrine disorder that resembles diabetes mellitus. In addition, the same research group demonstrated that insulin and insulin-like growth factor expression and function deteriorate with progression of AD being these effects linked to brain reductions in acetylcholine [32]. Therefore, the authors proposed the term, “Type 3 Diabetes” to reflect this pathogenic mechanism of neurodegeneration.

Furthermore, insulin has been shown to regulate the phosphorylation state of tau protein by regulating the activity of phosphorylating enzymes. Insulin concentration deficit increases the activity of glycogen synthase-3 kinase [33], which was found to cause tau hyperphosphorylation [19]. ATP acts in similar way, reduction of ATP activates both protein kinases erk36 and erk40 [34], which in turn causes tau hyperphosphorylation [35].

These data provide clear evidence that the metabolism of AβPP, Aβ degradation and tau protein phosphorylation are under control of insulin signal transduction.

3. Glucose/energetic metabolism deficiency in Alzheimer’s disease

Normal brain function requires a steady supply of energy substrate to carry out all of its cellular and molecular needs. Glucose is the primary source of fuel for any energy-demanding activity in brain that together with oxygen is delivered by the circulation for the metabolic chores that
keep brain cells healthy [36]. When glucose delivery to the brain stops, catastrophic neurological consequences or even death can develop. There is increasing amount of evidence suggesting that insulin present in CNS is a regulator of central glucose metabolism, similar to that observed in the periphery, even if it is considered that glucoregulation is not the main function of insulin in the brain (for review see [37]).

Early and severe abnormalities of cerebral glucose metabolism parallel worsening of the symptoms of dementia [38,39]. Late-onset AD is associated with glucose abnormalities distributed over all cortical areas, and particularly in parietotemporal and frontal association cortices [40,41]. This hypometabolism in the cerebral cortex is particularly pronounced in structures with both high glucose demands and insulin sensitivity (for review see [42]).

Recently, Kim et al. [43] reported that glucose hypometabolism of early onset AD patients is much greater in magnitude and extent than that of late onset patients, though both groups are similar in dementia severity. When the authors compared the decline of glucose metabolism with the Clinical Dementia Rating (CDR) stage, the slope was steeper in early onset than in late onset AD suggesting that the greater hypometabolism in early onset patients is required to reach the same severity of dementia.

These abnormalities in cerebral glucose utilization include a diminished activity of key enzymes involved in intermediary metabolism notably the activity of glutamine synthetase, creatine kinase, aconitase, pyruvate dehydrogenase and α-ketoglutarate dehydrogenase [44–46]. These enzymes are highly susceptible to oxidative modification and are altered by exposure to a range of pro-oxidants [47]. Reduced pyruvate dehydrogenase activity results in a decreased level of acetyl-CoA, and together with the diminished activity of choline acetyltransferase, the synthesis of acetylcholine in the presynaptic neuron is markedly reduced [48]. In this respect, it is noteworthy that the degeneration of the cholinergic system correlates with the progression of mental disturbances in patients with AD [49]. A decreased concentration of acetyl-CoA may also decrease the formation of intracellular cholesterol [50]. Cholesterol is the main sterol in membranes and is important for normal cell function. Cholesterol levels are markedly decreased in brain membranes and in the cerebrospinal fluid of AD patients [51–53]. Another decisive pathophysiological consequence of the markedly perturbed glucose metabolism is a decrease in ATP production from glucose by around 50% in the beginning of sporadic AD [54]. A fall in ATP formation in the sporadic AD brain has also been demonstrated by other investigators [55,56]. This energy deficit may compromise ATP-dependent processes in a hierarchical manner [57] including cellular and molecular mechanisms.

The most consistent defect in mitochondrial electron transport enzymes in AD has been a deficiency in cytochrome oxidase. There are several reports indicating a reduced cytochrome oxidase activity in AD platelets [58,59] and in post mortem brain tissue from patients with AD, particularly in neurofibrillary tangle-bearing neurons [60,61]. Previous studies have also demonstrated a perikaryal accumulation of cytochrome oxidase protein, immunolocalized to cytosol by immunoelectron microscopy in the face of reduced numbers of intact mitochondria. These results suggested that enhanced degradation of mitochondria occurs in AD, leaving behind lysosomal detritus containing non-functioning mitochondrial components [62]. Studies with cybrid cells demonstrated that deficits in cytochrome oxidase in AD platelets could be transferred to Rho cells, which retain the cytochrome oxidase deficit [63,64]. Additionally the resulting cybrid cells showed markedly increased free radical production, impaired intracellular calcium buffering, elevated basal cytosolic calcium concentration, and enhanced sensitivity to inositol 1,4,5-triphosphate-mediated calcium release [63,64]. Recently, Crouch and colleagues [65] found that Aβ42 specifically inhibited cytochrome oxidase of human mitochondria in a dose-dependent manner this effect being dependent on the presence of Cu²⁺. Altogether these data indicate that mitochondria dysfunction is a relevant event occurring in AD pathophysiology.

4. Mitochondrial dysfunction as a trigger of neuronal degeneration and death

Although the brain represents only 20% of the body weight, it receives 15% of cardiac output and accounts for 20% of total body oxygen consumption. This energy requirement is largely driven by neuronal demand for energy to maintain ion gradients across the plasma membrane that is critical for the generation of action potentials. This intense energy requirement is continuous; even brief periods of oxygen or glucose deprivation result in neuronal death.

Mitochondria are increasingly recognized as subcellular organelles that are essential for generating the energy that fuels normal cellular function while, at the same time, they monitor cellular health in order to make a rapid decision (if necessary) to initiate a programmed cell death. As such, the mitochondria sit a strategic position in the hierarchy of cellular organelles to continue the healthy life of the cell or to terminate it. These organelles are essential for neuronal function because the limited glycolytic capacity of these cells makes them highly dependent on aerobic oxidative phosphorylation for their energetic needs. However, oxidative phosphorylation is a major source of endogenous toxic free radicals, including hydrogen peroxide (H₂O₂), hydroxyl (HO⁻) and superoxide (O₂⁻) that are products of normal cellular respiration [66]. With the inhibition of electron transport chain, electrons accumulate in complex I and co-enzyme Q, where they can be donated directly to molecular oxygen to give O₂⁻ that can be detoxified by the mitochondrial manganese superoxide dismutase (MnSOD) to give H₂O₂ that, in turn, can be converted to H₂O by glutathione peroxidase (GPx). However, O₂⁻ in the presence of nitric oxide (NO⁻), formed during the conversion of
arginine to citrulline by nitric oxide synthase (NOS), can originate peroxynitrite (ONOO−). Furthermore, H2O2 in the presence of reduced transition metals can be converted to toxic HO• via Fenton and/or Haber Weiss reactions. Inevitably, if the amount of free radical species produced overwhelms the neuronal capacity to neutralize them, oxidative stress occurs, followed by mitochondrial dysfunction and neuronal damage. Reactive species generated by mitochondria have several cellular targets including mitochondrial components themselves (lipids, proteins and DNA). The lack of histones in mitochondrial DNA (mtDNA) and diminished capacity for DNA repair render mitochondria an easy target to oxidative stress events.

Mitochondria also serve as high capacity Ca2+ sinks, which allow them to stay in tune with changes in cytosolic Ca2+ loads and aid in maintaining cellular Ca2+ homeostasis that is required for normal neuronal function [67–69]. Conversely, excessive Ca2+ uptake into mitochondria has been shown to increase ROS production, inhibit ATP synthesis, release cytochrome c, and induce mitochondrial permeability transition [70–72]. The mitochondrial permeability transition (MPT) is defined as the sudden increase of inner mitochondrial membrane permeability to solutes of molecular mass less than 1500 Da [73,74]. Strong evidence now exists that the MPT is due to the opening of a nonselective megachannel (estimated to be 2–3 nm in diameter) [75,76]. Because the chemiosmotic theory is based on the inner membrane being impermeable to solutes that are not specifically transported, MPT would collapse the mitochondrial membrane potential (ΔΨm) and uncouple the electron transport system from the production of ATP. Additionally MPT results in mitochondrial swelling and can lead to the release of proapoptotic proteins. Importantly, Ca2+, Pi, oxidative stress, and low inner membrane potential promote the onset of MPT, whereas cyclosporin A (CsA), Mg2+, ADP, and the existence of a high membrane potential oppose the onset [74,77].

Mitochondrial dysfunction and the resulting energy deficit trigger the onset of neuronal degeneration and death.

5. Mitochondrial impairment links diabetes to Alzheimer’s disease

Increased oxidative stress has been implicated in the pathology of several diseases including diabetes and AD [78,79]. Evidence from the literature indicates that there is an increase in oxidative stress in human [80] and experimental diabetes [81,82] and a decrease in the antioxidant capacity [83,84].

Oxidative damage in rat brain is increased by experimentally induced hyperglycemia [85]. Schmeichel et al. [86] suggested that oxidative stress leads to oxidative injury of dorsal root ganglion neurons, mitochondria being a specific target. Recently, we observed that brain mitochondria isolated from streptozotocin (STZ) diabetic rats, a model of type 1 diabetes, possess a lower content of coenzyme Q9 (CoQ9) indicating a deficit in antioxidant defenses in diabetic animals and, consequently, an increased probability of oxidative stress occurrence [87]. The reduced form of CoQ may function as an antioxidant, protecting membrane phospholipids and serum low-density lipoprotein from lipid peroxidation by quenching lipid radicals or lipid peroxidation initiating species and, it also protects mitochondrial membrane proteins and DNA from free radical-induced oxidative damage [88–90].

Diabetes and AD are associated with impaired glucose utilization, deficits in mitochondrial activity and metabolic dysfunction [91–93]. Inhibition of cellular energy production has been shown to reduce or abolish both insulin secretion and action [94]. In addition, the decrement in oxidative phosphorylation (OXPHOS) efficiency is related to a loss in the control of glucose homeostasis as evidenced by the increase in tissue and blood lactate levels, as well as by the change in glucose tolerance. Cybrid cells constructed from individuals with maternally inherited diabetes exhibited lactic acidosis, poor respiration and marked defects in mitochondrial morphology and respiratory chain complex I and IV activities [95].

Diabetes mellitus leads to functional and structural changes in the brain, which appear to be most pronounced in the elderly. Furthermore, increased age is associated with insulin resistance [96]. Increasing data support the idea that mitochondrial function declines with aging and in age-related diseases such as diabetes and AD [92,97]. Data from our laboratory show the existence of an age-related impairment of the respiratory chain and an uncoupling of OXPHOS in brain mitochondria isolated from Goto-Kakizaki (GK) rats, a model of type 2 diabetes [98]. Furthermore, we also show that aging exacerbates the decrease in the energetic levels promoted by diabetes [98]. The maintenance of OXPHOS capacity is extremely important in the brain since about 90% of the ATP required for the normal functioning of neurons is provided by mitochondria. Because CNS depends so heavily on ATP production, the inhibition of OXPHOS will affect this system before any other system. For example, CNS requires a large amount of ATP for the transmission of impulses along the neural pathway, thus mitochondrial function impairment will result in neurodegeneration and loss in neuronal metabolic control [92,97].

ΔΨm, which normally accounts for 80% of the proton-motive force, contributes for the high degree of reduction of the matrix NADPH/NADP+ pool and, in turn, this pool helps to maintain the matrix glutathione pool in the reduced state. We observed that the maintenance of ΔΨm in mitochondria isolated from STZ rats is correlated with the unchanged content of reduced glutathione (GSH) [87]. GSH is abundant in mitochondria and is a first-line defense in the cellular antioxidant system. Baydas et al. [99] reported that although STZ diabetic rats present higher levels of lipid peroxidation in hippocampus, cortex and cerebellum as compared to control rats, no significant alterations are found in GSH levels in the same brain regions.
As previously discussed, mitochondria are also important cytoplasmic Ca²⁺ buffers since they avoid the increase of Ca²⁺ above a critical value termed “set-point”. In oxidative stress conditions, a sustained increase in intracellular Ca²⁺ concentration occurs [100] and the cytosolic Ca²⁺ levels play a role in the modulation of several intracellular signalling pathways, including protein kinase C-α and calmodulin-dependent signalling [101], which have also been implicated in apoptotic processes. The cytosolic Ca²⁺ level can be increased by ROS in various cell types through the mobilization of intracellular Ca²⁺ stores and/or through the influx of extracellular Ca²⁺ [102]. The maintenance of Ca²⁺ homeostasis represents a major expenditure within neurons and, through respiratory control mechanisms, is tightly coupled to the rates of OXPHOS and the generation of ROS. We observed that diabetes decreases the capacity of mitochondria to accumulate Ca²⁺, a favourable intracellular environment for MPT opening [87,98]. Furthermore, our data are in agreement with the “Calcium hypothesis” which first proposes that among the many biochemical and histological changes involved in brain aging and in age-related diseases, Ca²⁺ alteration is a central defect [103,104]. Accordingly, we observed that brain mitochondria of GK rats present an age-related susceptibility to Ca²⁺, indicating that aging predisposes the diabetic rats’ mitochondria to the opening of MPT. The MPT opening might be also associated with osmotic swelling of mitochondria leading to structural changes of these organelles. Indeed, in peripheral nerves of diabetic humans, the existence of mitochondrial ballooning and disruption of internal cristae is observed, although this is localized to Schwann cells and is rarely observed in axons [105]. Similar structural abnormalities in mitochondria have been described in Schwann cells of galactose-fed rats [105] and dorsal root ganglion neurons of long-term STZ diabetic rats [106]. One current hypothesis is that high glucose concentrations induce elevated levels of OXPHOS, resulting in damaging amounts of ROS that lead to changes in mitochondrial structure and function [107].

Accumulating evidence suggests that mitochondrial dysfunction is intimately associated with AD pathophysiology. Furthermore, Lustbader et al. [108] reported that Aβ interacts with Aβ-binding dehydrogenase (ABAD) in mitochondria obtained from AD patients and transgenic mice brains, which suggests that ABAD is a direct molecular link from Aβ to mitochondrial toxicity. More recently, the same group reported that ABAD enhances Aβ-induced cell stress via mitochondrial dysfunction [109]. Another study also showed that Aβ is present in mitochondria and, in the presence of copper, inhibits cytochrome oxidase [65]. AβPP has also been associated with the outer mitochondrial membrane [110]. Furthermore, it has been shown that an IDE isoform, which regulates Aβ levels, is targeted to mitochondria [111]. There is also evidence that β-secretase is present in these organelles [112]. In addition, we have demonstrated that a functional mitochondria is required for Aβ-induced neurotoxicity, as investigated using ρ+ and ρ0 mitochondrial DNA depleted cells [113].

Studies from our laboratory show that Aβ inhibits the respiratory chain complexes and reduces ATP levels in PC12 cells [114,115]. We also showed that Aβ40 and Aβ25-35 impair the respiratory chain, uncouple OXPHOS, decrease the energetic levels and exacerbate the susceptibility of isolated brain mitochondria to MPT opening [87,98,116]. However, we observed that Aβ exacerbatates Ca²⁺-induced opening of MPT without inducing the permeability per se [117,118]. Recently, we observed that CoQ10 treatment attenuates the decrease in OXPHOS efficiency induced by Aβ40 [116]. CoQ10 is a key component of the mitochondrial electron transport chain (ETC) that not only serves as the electron acceptor for complexes I and II of the ETC but is also a potent antioxidant. Indeed, recent findings from our laboratory show that CoQ10 treatment avoids the increase in H2O2 production induced by Aβ40 [116]. Previously, in vitro studies have shown that Aβ-mediated cell death in both neuronal and non-neuronal cells is mediated in part by the increase in cellular H2O2 [119] and that catalase has a protective role as an H2O2-degrading enzyme [120]. Furthermore, we observed that several other antioxidants (vitamin E, idebenone, and reduced glutathione), melatonin and nicotine showed protective effects by improving the activity of the respiratory chain complexes and maintaining ΔΨm and cellular energetic levels [113].

Recent findings [121] indicate that insulin is a major regulating factor of mitochondrial OXPHOS in human skeletal muscle. Previously, Boirie and collaborators [122] reported that insulin selectively stimulates mitochondrial protein synthesis in skeletal muscle and activates mitochondrial enzyme activity. However, a direct stimulatory action on ATP production was not shown. Our results are in accordance with these data because although we do not observe any significant change on ATP content, insulin treatment increases mitochondrial OXPHOS efficiency [87]. In this line, Gustafsson et al. [123] reported that (IGF-1) protects from hyperglycememia-induced oxidative stress and neuronal injuries by regulating ΔΨm, possibly by the involvement of uncoupling protein 3 (UCP3). Similarly, Huang et al. [124] reported that insulin prevents depolarization of the mitochondrial inner membrane in sensory neurons of type 1 diabetic rats. Furthermore, insulin was capable to increase mitochondrial antioxidant defenses (CoQ9 content) that had been reduced by diabetes. Growing evidence suggests the importance of insulin and (IGFs) in intracellular antioxidant status by playing a pivotal role in protein kinase B-mediated expression of Bel2 protein, that prevents the escape of ROS by opposing the oxidative-stress-induced pro-apoptotic action of Bax [125]. Another study showed that pre-treatment of cells with IGF-1 suppresses H2O2-induced apoptosis by subsequent inhibition of Bax expression [125,126]. Recently, Duarte et al. [127] reported that insulin protects cortical neurons against oxidative stress
this effect being due to the modulation of glutathione redox cycle.

Our data also indicate that insulin is capable to increase the capacity of mitochondria to accumulate Ca\(^{2+}\) suggesting a role of insulin in Ca\(^{2+}\) homeostasis. Moreover, it has been shown that insulin modulates the cellular clearance of A\(\beta\) [21] and IGF-1 protects neurons against its neurotoxic effects [128]. Recently, Rensink and colleagues [129] reported that insulin inhibits A\(\beta\)-induced cell death in cultured human brain pericytes. In accordance, our data indicate that insulin treatment also protects against mitochondrial injury induced by A\(\beta\)40 [87].

Data discussed above are consistent with the view that diabetes-related mitochondrial dysfunction is exacerbated by aging and/or by the presence of neurotoxic agents, such as A\(\beta\), suggesting that diabetes and aging are risk factors for the neurodegeneration induced by these peptides. An association between diabetes and AD has long been recognized. Here we presented evidence that the association between diabetes and AD signifies a common underlying pathology, in this case, mitochondrial dysfunction. However, we also showed that mitochondrial dysfunction can be avoided/reduced by insulin and antioxidants. Although insulin does not affect basal mitochondria function, in the presence of A\(\beta\) insulin prevents a drastic decline in mitochondrial OXPHOS efficiency and avoids an increase in the oxidative stress, improving and/or preserving the function of neurons under adverse conditions. Given the importance of mitochondria as primary source of oxidative stress in AD and diabetes, the use of antioxidants may also be useful. However, the broad occurrence of both diseases, the non-regenerative nature of the CNS and the fact that AD diagnosis often does not occur until late in disease progression, suggest that the ideal antioxidant should be used as prophylactic treatment in aged population.

References


