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The Interplay Among Oxidative Stress, Brain Insulin Resistance and AMPK Dysfunction Contribute to Neurodegeneration in Type 2 Diabetes and Alzheimer Disease

Eugenio Barone[a], **Fabio Di Domenico**[a], **Marzia Perluigi**[a], **D. Allan Butterfield**[b,*]

[a]Department of Biochemical Sciences "A. Rossi-Fanelli", Sapienza University of Rome, Piazzale A. Moro 5, 00185, Roma, Italy

[b]Department of Chemistry and Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, 40506-0055, USA

Abstract

Alzheimer's disease (AD) is the most common form of dementia in the elderly followed by vascular dementia. In addition to clinically diagnosed dementia, cognitive dysfunction has been reported in diabetic patients. Recent studies are now beginning to recognize type 2 diabetes mellitus (T2DM), characterized by chronic hyperglycemia and insulin resistance, as a risk factor for AD and other cognitive disorders. While studies on insulin action have remained traditionally in the domain of peripheral tissues, the detrimental effects of insulin resistance in the central nervous system on cognitive dysfunction are increasingly being reported in recent clinical and preclinical studies. Brain functions require continuous supply of glucose and oxygen and a tight regulation of metabolic processes. Loss of this metabolic regulation has been proposed to be a contributor to memory dysfunction associated with neurodegeneration. Within the above scenario, this review will focus on the interplay among oxidative stress (OS), insulin resistance and AMPK dysfunctions in the brain by highlighting how these neurotoxic events contribute to neurodegeneration. We provide an overview on the detrimental effects of OS on proteins regulating insulin signaling and how these alterations impact cell metabolic dysfunctions through AMPK dysregulation. Such processes, we assert, are critically involved in the molecular pathways that underlie AD.

Keywords

Alzheimer disease and type 2 diabetes; oxidative and nitrosative stress; insulin resistance; neurodegeneration; biliverdin reductase-A; AMP-activated protein kinase

*Corresponding author: Prof. D. Allan Butterfield, Department of Chemistry and Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, 40506-0055, USA, Ph: +1(859) 257-3184, dabcns@uky.edu.

Conflict of interest

The authors declare no conflict of interest exists with any author.

1. Introduction

The ever-increasing life expectancy has led to a dramatic increase in the prevalence of age-associated disorders, including type 2 diabetes mellitus (T2DM) and age-related dementia and Alzheimer disease (AD). Notably, there is a growing body of epidemiological evidence suggesting that metabolic syndrome and T2DM increase the risk of developing age-related cognitive decline, mild cognitive impairment (MCI), vascular dementia, and AD (reviewed in [1]).

Although the brain only represents 2% of the body's total weight, it has a high demand for energy compared to other tissues, largely attributed to the extremely active and complex processes involved in neuronal transmission [2]. Neurons are a paramount example of high energy expenditure for their function and survival. This situation is reflected in large metabolic rates in neurons and by the comparatively higher sensibility of brain tissues to oxygen and glucose deprivation. Reactions controlling the conversion of nutrients into available cytosolic levels of ATP are critical to generate the potential metabolic work that is available to a neuron at any given time [3, 4].

Approximately 70% of the total energy is consumed for regulation of neuronal signaling (resting and action potentials, postsynaptic receptor signaling, the glutamine cycle, and postsynaptic Ca^{2+}), and approximately 30% is used for non-signaling conduction activities (proteins, phospholipids, etc.). Indeed, failure to maintain basal energy levels can result in synaptic loss and cognitive impairment within few minutes, thus rendering the brain highly vulnerable to energy deficit-mediated damage [5, 6].

Among energy fuels, glucose is an essential substrate for the adult brain, and at least 25% of consumed glucose is used to drive basal brain activities [7]. Glucose metabolism sustains the physiological functions of the brain through glycolysis and mitochondrial oxidative phosphorylation (OXOPHOS), and its product, ATP, is the electrochemical basis for the maintenance of neurons and non-neuronal cells. Therefore, glucose metabolism and mitochondrial functions are essential ATP sources crucial for neuronal homeostasis [7].

Neuronal glucose utilization includes mechanisms that control its uptake. This involves glucose specific transporters (GLUTs), insulin signaling pathways and the entry of glycolytic metabolites into mitochondria that are further oxidized into the Krebs cycle [7].

Glucose import into the brain from the circulation is primarily mediated through the insulin-insensitive GLUT1, which is expressed by endothelial cells and astrocytes at the blood brain barrier (BBB) [8]. Within the brain parenchyma, GLUT3 and GLUT1, both of which are considered insulin-insensitive, are expressed widely by neurons and glial cells, respectively [8].

There is also evidence to support some functions of insulin in regulating brain glucose uptake. Indeed, several studies have been focused to unravel the pathological mechanisms and clinical implications that result from aberrant insulin signaling- i.e insulin resistance- both in the brain and periphery [8] (Figure 1). While much is known about the molecular aspects underlying insulin resistance in metabolic disorders, including obesity and T2DM,

the exact mechanisms through which aberrant insulin signaling leads to cognitive decline need to be further elucidated.

In addition, living cells display multiple complementary mechanisms for regulation of energy homeostasis. Changes in the ATP/AMP gate the activity of multiple metabolic sensors which, in turn, induce a specific signaling cascade for short and long-term adaptations of neuronal functions. For example, all known eukaryotic cells, including neurons, harbor energy sensors, such as AMP-activated protein kinase (AMPK), which tend to restore ATP concentrations by decreasing anabolic and/or energy consuming processes, while increasing energy production through catabolism of post-energy challenges [9]. In model systems, sustained decreases in AMPK activity accompany insulin resistance, whereas AMPK activation increases insulin sensitivity. As well, activation of AMPK decreases endoplasmic reticulum (ER) stress and oxidative stress OS, and activates autophagy, all of which appear to be involved in the pathogenesis of insulin resistance [10].

In the sections of this review below, we discuss the interplay among OS, brain insulin resistance and AMPK dysfunctions to provide mechanistic insights into characterization of neuronal energy metabolism impairment, a key event for neurodegeneration both in T2DM and Alzheimer disease (AD) [11].

2. Alzheimer disease

Neurodegenerative disorders, including AD, share several pathological features, among which, bioenergetic defects are prominent characteristics [11]. AD is the predominant form of dementia affecting the elderly, and AD causes progressive degeneration of the brain. At the cellular level, AD is marked by a selective and progressive loss of nerve cells, dendritic spines and synapses, impaired neurotransmission, and progressive isolation of remaining nerve cells [12]. Neuropathologically, AD is characterized by deposition of extracellular β-amyloid ($A\beta_{40}$ and $A\beta_{42}$) in the brain parenchyma forming neuritic (senile) plaques (SPs), the presence of $A\beta_{42}$ oligomers, β-amyloid angiopathy around cerebral blood vessels, and intraneuronal deposits of hyper-phosphorylated, abnormally conformed, and truncated tau protein in the form of neurofibrillary tangles (NFTs) [13].

Accumulating evidence indicates that in the development of AD, pathophysiological changes can occur up to 20–30 years before clinical symptoms manifest [14]. The limited amount of information regarding early stages of the neurodegenerative process, combined with to the fact that the disease's clinical features that can lead to a diagnosis of AD occur at relatively advanced stages at which the degenerative processes have reached thresholds, emphasize the urgent need to identify the molecular aspects of the disease that are initiated in the pre-symptomatic stages.

Among putative candidates for such needs, emerging studies reveal that defects of energy metabolism, including glucose metabolism and mitochondrial activities, initiate many years before clinical manifestation of AD [15]. For example, with age, neuronal glucose uptake and proper mitochondrial function decline, reducing OXOPHOS activity, promoting

increased oxidant species production [10]. These events reportedly occur decades before the onset of clinical symptoms of AD, exemplified in a study performed on young adults at high risk of developing AD [16].

Published reports indicate that global cerebral glucose metabolic rate is decreased by 20–25 % in AD patients, with the earliest change registered being in the hippocampus. In the 1980s, fluorodeoxyglucose positron emission tomography (FDG PET) studies showed brains from AD patients used less glucose than those from control subjects [17–21]. PET studies also showed decreased oxygen consumption by AD brains [22]. These studies elevated interest in a potential metabolic component for this disease. In addition, biochemical studies demonstrated activity deficiencies in bioenergetic-related enzymes such as Complex IV (cytochrome c oxidase), suggesting a mitochondrial defect [23].

While ^{18}F-FDG PET studies have shown reduced brain glucose uptake in regions vulnerable to AD pathology [18–21], it is unclear whether an overall failure of regulation of brain glucose metabolism is a key etiopathogenic factor in AD and whether abnormalities of brain glucose homeostasis in AD are related to peripheral glucose concentration. Abnormalities in brain glucose homeostasis are intrinsic to AD pathogenesis and begin several years prior to clinical symptoms [14]. Interestingly, in a recent study by An and colleagues it has been reported that higher brain tissue glucose concentration, reduced glycolytic flux and lower levels of GLUT3 are related to severity of AD pathology and the expression of AD symptoms [24]. In addition, increasing fasting plasma glucose levels (but not the hyperglycemia as observed in T2DM individuals) are associated with higher brain tissue glucose concentrations [24]. Indeed, the longitudinal associations between fasting plasma glucose and brain tissue glucose concentrations are not driven by individuals with T2DM [24]. Hence, these observations suggest that it is not so much hyperglycemia as just reduced brain metabolism that favors higher brain glucose levels and related neurotoxicity in AD [24].

Furthermore, neuronal glucose hypometabolism negatively regulates the metabolic capacity of cells and leads to increased OS levels [17]. Moreover, modifications of key enzymes involved in glycolsis and in the Krebs cycle are probably major contributors to the hypometabolism observed in AD [11, 25]. Our group contributed this notion by demonstrating that aldolase, triosephosphate isomerase, glyceraldehyde-3-phosphate dehydrogenase, phosphoglycerate mutase 1 and α-enolase are oxidatively damaged in brain areas affected by AD pathology [11, 25]. Further, oxidatively modified aconitase, creatine kinase and ATP synthase are also present, which may contribute to the reduced glucose metabolism and ATP production in mitochondria [25]. Accordingly, several studies have shown that AD patients exhibit very early signs of metabolic changes in neurons and glial cells [11].

3. Type 2 diabetes mellitus

As well as growing older, a significant fraction of the populations of the developed economies also are obese and sedentary. Although this is most marked in the developed nations, it is truly an international trend. In addition, since many children in developed

nations show dramatic increases in body mass index (BMI), this is a deeply concerning indicator of future health problems [26, 27]. For example, obesity increases risk of cancers, cardiovascular disease, and metabolic syndromes including T2DM [26, 27]. According to the International Diabetes Federation, T2DM affects 246 million people worldwide with an expected prevalence of 380 million by 2025, representing as much as 7.1% of the global adult population.

T2DM is a metabolic disease characterized by the relative resistance to peripheral insulin action, resulting in impaired glycemic control. Although genome-wide association studies have revealed that certain single nucleotide polymorphisms (SNPs) related to beta-cell function predispose one to the development of T2DM [28, 29], clinical characteristics such as obesity and lack of physical activity are regarded as the most important risk factors [30]. These latter predispose people to metabolic changes, which accumulate over the time and drive the inflammation and cell stress, leading to insulin resistance and ultimately to T2DM [30].

T2DM individuals show reduced glucose uptake/metabolism in the brain as measured by ^{18}F-FDG PET scanning [31–35]. Interestingly, while non-diabetic subjects show a positive association between basal and glucose-stimulated insulin secretion and brain glucose uptake during euglycaemic-hyperinsulinaemic clamp, no such association was observed in T2DM individuals, thus suggesting that insulin resistance may contribute to reduced brain glucose uptake/metabolism in T2DM [31, 32]. On the other hand, as proposed by others, this phenomeon may represent an adaptative response to reduce the brain's exposure to excessive circulating levels of glucose [35]. T2DM might be associated with defects in cerebral glucose metabolism stemming from decreased glucose transport across the BBB, a finding that might limit the brain's ability to sense and respond appropriately to increments in peripheral glucose [31–35]. This defect may be driven by increasing insulin resistance, leading to further blunting of the brain glucose response to elevations in peripheral glucose [31–35]. In addition to that, Backestrom et al. reported that hyperglycemia affects neuronal and behavioural functions in participants with T2DM when their working memory is challenged, thus suggesting that working memory and the ability to perform complex activities during hyperglycaemic episodes are compromised [31].

In different clinical studies, an association of T2DM and neurodegenerative disorders as well as decline in memory has been described. A series of longitudinal studies reported that glucose intolerance and impairment of insulin secretion are associated with a higher risk to develop dementia or AD [36–38]. Indeed, it was shown that MCI subjects with normoglycemia at baseline had less functional and global cognitive decline, less whole-brain volume loss and lower conversion to AD than MCI subjects with impaired glycemia over 2 years of observations [39].

Vascular complications might only partially explain the increased incidence of neurodegeneration observed in patients with T2DM. Among others, the causes could be impaired β-amyloid (Aβ) clearance [40], up-regulation of amyloid precursor protein (APP) expression and Aβ deposition [41], or hyperinsulinemia that is present in T2DM. It is reported that such changes may play an important role in the formation of senile plaques

[42]. On the other hand, patients with AD more frequently present with an impaired glucose metabolism or T2DM [43]. In addition, to further complicate this quite intricate puzzle, not all people developing AD show metabolic disorders as a comorbidity [1].

Hence, these observations raise questions thus far unanswered: whether T2DM is a cause, consequence, or compensatory counter-regulation to neurodegeneration, and whether neuronal insulin resistance indeed represents a risk factor for AD?

4. Insulin resistance links T2DM and AD

An important link between T2DM and the various forms of dementia lies is alterations of insulin signaling, particularly at the cerebral level. This process, named brain insulin resistance, negatively impacts memory functions by impairing the metabolic fueling of neurons that become dysfunctional [1]. Of note, the brain is an insulin-sensitive organ, in which insulin, beyond participating in glucose transport/metabolism, also regulates metabolic pathways required for the maintenance of memory and learning processes that are disrupted both in T2DM and in AD [44]. Consistent with this observation, systemic infusion of insulin under euglycemic hyper-insulinemic conditions in healthy humans demonstrated improvement with verbal memory and selective attention [45] suggested to be due to improved consolidation of information [46]. Likewise, intranasal insulin improves memory in both healthy humans and many patients with Alzheimer's disease [47–49].

Conversely, insulin resistance is a condition characterized by a relative inability of target tissues to respond to the action of insulin. As a systemic disorder, insulin resistance locally affects several insulin-responsive tissues, such as adipose tissue (AT), liver and muscles, which are not able to correctly regulate glucose homeostasis [50]. AT inflammation and dysfunction is one of the major causes of disruption of the insulin signaling cascade in obesity and also represents a central trigger for development of insulin resistance in T2DM [51–54]. A similar inflammatory process is thought to occur also in the brain finally leading to brain insulin resistance [55]. In the brain, glial cells, especially astrocytes and microglia, undergo activation under pro-inflammatory conditions. Unchecked or chronic inflammation therefore becomes deleterious, leading to progressive neuronal damage [56].

Other than inflammation, increased OS levels were demonstrated to impair the activation of insulin signaling at the cellular level, thus representing an additional triggering mechanism in the development of insulin resistance both in T2DM and AD [57].

Because of these similarities, metabolic disorders (obesity and T2DM) and AD are pathological conditions that can provide insights into shared molecular mechanisms that lead to systemic and brain insulin resistance, as well as their interplay.

5. Molecular mechanisms driving development of brain insulin resistance

Most of the information collected until the present regard the development of systemic insulin resistance that is phenotypically characterized by: (i) an early phase during which hyperinsulinemia overcomes the initial reduction of glucose uptake and thus maintains an euglycemic state (pre-diabetes); and (ii) a late phase in which insulin resistance persists,

hepatic glucose production rises, and endogenous insulin production falls, resulting in fasting and postprandial hyperglycemia [58]. Within this scenario, the epidemiological association of T2DM with cognitive dysfunction ranging from MCI to manifest dementia was shown [59]. This association already starts in midlife; and the longer the duration of diabetes, the higher the risk for developing slight cognitive impairment and eventually dementia [59]. Mostly importantly, cognitive decline seems to start well ahead of the manifestation of overt diabetes, in the prediabetic state [60]. During the MCI stage, peripheral insulin resistance was found to be associated with glucose dysmetabolism in different brain areas, with significant differences between individuals who progress to AD compared to those who did not [61]. In addition, genetic models of T2DM (including db/db mice), pharmacologically-induced T2DM models (such as streptozotocin-treated mice) and rodents fed a high-fat diet develop systemic insulin resistance, hyperglycemia and strong biochemical evidence of brain insulin resistance, coupled with memory deficits, synaptic abnormalities (structural, molecular and neurophysiological) and other brain abnormalities [62–65]. These lines of evidence support the hypothesis that peripheral insulin resistance might trigger the development of brain insulin resistance that is an early neuropathological mechanism leading to T2DM-associated cognitive decline.

Although peripheral alterations in metabolic disorders might drive development of brain insulin resistance and dementia, brain insulin resistance also can develop independently, while representing – similar to metabolic disorders – an early neuropathological aspect of neurodegenerative diseases [1]. Consonant with this observation, development of brain insulin resistance was reported to be evident during the early phases of AD in post-mortem brain from amnestic MCI (aMCI) [66, 67]. Markers of brain insulin resistance such as the levels of inhibited IRS1 (phosphorylated IRS1 at residue Ser636) were found to be significantly associated with cognitive decline and such association was even stronger than those observed for canonical hallmarks of AD, i.e., Aβ and Tau [66]. Furthermore, a recent study by Kapogiannis and colleagues reported that increased levels of inhibited IRS1 evaluated in neuronal-derived extracellular vesicles were among the strongest individual predictors for the development of AD in the general population [68]. For these reasons, understanding how brain insulin resistance develops represent a key challenge for future studies.

The precise molecular mechanisms underlying the development of insulin resistance have not been completely elucidated. Under physiological conditions, the activation of insulin signaling requires the binding of insulin to its receptor (IR), which auto-phosphorylates and promotes the phosphorylation of its substrate, insulin receptor substrate 1 (IRS1) on specific Tyr residues (e.g. 612 and 632). Once activated, IRS1 works as a scaffold protein driving the activation of the two main arms of the insulin signaling: 1) the PI3K/PDK1/Akt pathway; and 2) the MAPK pathway [69] (Figure 1). In peripheral tissues, the former is critical for linking IRS1 to the metabolic actions of insulin. Indeed, Akt activation induces downstream signaling, which leads to the regulation of a network of genes controlling: (i) glucose uptake and metabolism; (ii) lipid metabolism; and (iii) protein metabolism [69]. The latter, Ras–MEK–ERK1/2 signaling, predominantly controls cell growth and differentiation [69, 70]. In the brain, the activation of the PI3K/PDK1/Akt axis also is involved in the maintenance of synaptic plasticity and memory consolidation [71], synthesis of nitric oxide, which, in

turn, plays a role in learning and memory processes [72]; in contrast, the MAPK cascade activation is responsible for the induction of several genes required for neuronal and synapse growth, maintenance and repair processes, as well as serving as a modulator of hippocampal synaptic plasticity that underlies learning and memory [73] (Figure 1). Both in metabolic disorders (obesity and T2DM) and AD, the uncoupling between IR and IRS1 occurs at the cellular level, leading to the inability of insulin to promote its cellular downstream effects (Figure 2). Thus, insulin resistance is characterized by the downregulation of IR expression and/or the inactivation of IRS proteins, the latter mediated by the phosphorylation of specific Ser residues (307, 312, 636). The aberrant activation of TNF-α receptor and stress-regulated kinases [i.e., JNK, IKkB, and PKR] as well as endoplasmic reticulum (ER) stress (PKR-mediated phosphorylation of eIF2α-P), are known mediators of IRS1 inactivation [56] (Figure 2).

However, all the above-mentioned proteins are down-stream effectors shared by several signaling pathways i.e., lipid metabolism and inflammation, and thus are not exclusively related to insulin signaling, although IRS1 is among their substrates [74]. Indeed, their involvement in insulin resistance requires the activation of other pathways. Furthermore, increased inflammation is a condition sufficient, but not necessary, during the development of insulin resistance, since disruption of inflammatory pathways by JNK deletion did not attenuate the pathological features of the early stage of systemic insulin resistance [75].

These fascinating aspects open new frontiers in the comprehension of the early mechanisms promoting the development of insulin resistance. Studies from our group showed that increased OS levels are antecedent to the rise of TNF-α in the brain of a mouse model of AD [76] and leads to the inactivation of IRS1 *in vitro* [76], thus suggesting a direct role in the development of brain insulin resistance. The increase in ROS levels inhibits the cellular production of ATP and decreases insulin secretion and sensitivity [77]. Similarly, oxidative damage affects a variety of signaling pathways related to the unfolded protein response and protein degradation, which could lead to insulin resistance [78, 79]. Moreover, previous studies have found that age-related mitochondrial disorders increase OS in individuals with T2DM, contributing to the development and progression of AD neuropathology [80–82].

6. Oxidative stress as an early event in the development of brain insulin resistance

Reactive species, especially ROS such as superoxide radical anion, hydrogen peroxide, and hydroxyl radical ions [83], are major contributors to OS. ROS produced endogenously have a physiological significance at low levels, especially in signaling pathways [84], while these mechanisms are not precisely understood because of the dual roles ROS play as both signaling and damaging agents.

With regard to the insulin signaling, previous studies suggested that a yet unknown intermediate stage during the IR activation process, the so-called redox priming step, exists in which oxidants like hydrogen peroxide (H_2O_2) facilitate, while some antioxidants such as butylated hydroxyanisole (BHA) or N-acetyl-cysteine (NAC) inhibit the insulin-induced IR autophosphorylation and thus activation [85]. An oxidative modification of cysteine

residues within the IR was proposed as the structural basis of the “redox priming”, with Cys1138 in the proximity of catalytic aspartate 1132 being the most prominent candidate for the priming, since the non-oxidizable IR mutant Cys1138Ala was the only IR cysteine mutant that showed defective kinase activity in functional experiments [86]. The idea of redox priming was supported by the finding that insulin stimulation itself leads to generation of endogenous H2O2 in fat cells [87, 88]. Therefore, insulin-induced H_2O_2 could be the priming factor facilitating IR autophosphorylation *in vivo*. A subsequent study found that the role of H_2O_2 is not restricted to the redox priming of IR, but also includes inhibition of protein tyrosine phosphatase PTP1B, which inactivates the IR by dephosphorylating A-loop phosphotyrosine [89]. Collectively, insulin-induced H_2O_2 plays a role of a net positive regulator of IR activation through its concerted actions on the opposite activities of IR tyrosine kinase and PTP1B phosphatase. Similar results were also reported in neuronal cells in which insulin stimulation generated a spike in H_2O_2, while NAC, a Gpx1-dependent H_2O_2 scavenger, completely abrogated both the insulin-induced H_2O_2 and autophosphorylation of IR at Y1150/Y1151, thereby suggesting that the H_2O_2 signal is a critical requirement for the activation of the IR in neurons [90].

In addition to the mechanisms outlined above, age-associated increased OS levels along with reduced glutathione (GSH) levels were reported in both human [91] and animals, the latter including either AD-relevant [92] or aging-relevant models [92]. Similarly, insulin resistance and T2DM mice showed increased OS markers and reduced GSH levels in the brain [78, 93–97], thus suggesting a close link among OS, development of brain insulin resistance, and cognitive dysfunction. Consistent with this suggestion, brain plasticity, the capability of the brain to undergo structural and functional changes in response to environmental stimuli, is finely modulated by diet and nutrient-dependent hormones, including insulin [98]. Accordingly, alteration of insulin signaling into the central nervous system may accelerate brain aging, affect brain plasticity and promote synapse loss and neurodegeneration [99].

Intriguingly, synapse loss was found to correlate with increased OS levels, thus accounting for pathological changes observed during the clinically silent prodromal phases of AD [100]. OS has been widely recognized as a prodromal factor associated with AD neurodegeneration [11, 101, 102]. Multiple factors mainly related to mitochondrial dysfunction and energy metabolism deficit contribute to elevate cellular OS [103]. Brain structure, significant unsaturated lipid composition, high oxygen consumption, relatively high levels of redox-active transition metal ions (Fe^{2+} and Cu^{+}), and rapid metabolic rate all contribute to brain susceptibility to toxic effects of OS. Moreover, the natural process of aging is associated with a physiological increase of OS over time [104–106]. As individuals age, ROS are integrated, to some extent, in the aging brain, disrupting redox-related communication and leading to cellular alterations, such as senescence and cell death, due to the inability to maintain redox homeostasis. This equilibrium in the cell is particularly important to keep the balanced microenvironment needed for multiple biological processes, from bioenergetics to vesicle transport and intracellular signaling. Further, oxidative damage is greater in aged brains than it is in younger brains [107–111]. Notably, this “physiological accumulation” of oxidative damage with aging is exacerbated during neurodegeneration and is associated with loss of cognitive functions [112]. At the neuronal level, oxidative damage related to aging,

strongly impairs synaptic components involved in neuronal plasticity, cytoskeletal dynamics and cellular communication, among other alterations [111, 113, 114].

Such impairment also may occur at the expense of the insulin signaling cascade, thus triggering development of brain insulin resistance. In T2DM, consistent hyperglycemia, excessive lipid and high-level advanced glycation end products (AGEs) lead to ROS production [115]. In contrast, oxidative conditions-induced formation of AGEs and oxidation of other molecules [116], leading to cellular dysfunction, including impaired energy metabolism, altered cell signaling and cell cycle, impaired cell transport mechanisms and overall dysfunctional biological activity, immune system over-activation and inflammation [11, 116, 117]. Within this picture, it is interesting to note that levels of multiple DNA base oxidation products were found to be elevated in white blood cell DNA from patients with type II diabetes as compared with age-matched controls [118]. Similarly, oxidative stress-induced DNA fragmentation was observed among different brain regions in rats who developed diabetes [119]. Whether oxidative DNA damage plays a role by decreasing transcription of essential proteins involved in glucose metabolism in T2DM brain represent an intriguing hypothesis to be elucidated.

All these with cross-talk between AGEs and their receptors (RAGE) have been involved in the pathogenesis of diabetes, and a number of severe diabetic complications, including retinopathy, nephropathy, cardiovascular disease and nervous system dysfunction [120]. With the progression of T2DM, the increased OS and the reduced capacity of antioxidant defense can particularly damage both β-cells and neurons, resulting in progression of T2DM and related dementia [121].

Several reports highlight a close connection between insulin resistance and defects in energy metabolism driven by OS [57, 80, 122–125]. AD patients show reduced brain IR sensitivity [66, 126], hypophosphorylation of the IR, and downstream second messengers such as IRS1 [67, 80, 127, 128]. Increased OS levels in AD promote multiple effects, including the inhibition of cellular energy production, and the reduction of both insulin secretion and sensitivity [11, 77, 129]. In turn, defective insulin signaling-associated impairment in glucose uptake and utilization leads to a vicious cycle, in which reduced energy production parallel increased ROS and RNS levels that contribute to oxidative/nitrosative damage to mitochondria [80, 130]. In that regard, previous studies reported that brain insulin resistance, promotes an increase of mitochondrial ROS levels finally leading to neuronal apoptosis [131–134]. Furthermore, mitochondrial ROS overproduction enhances the accumulation of Aβ peptides and induces oxidative damage to proteins, lipids and nucleic acids in the brain under insulin resistance conditions [135–138]. In addition, brain is one of the most cholesterol-rich organs, and cholesterol oxidation products, i.e., oxysterols (e.g., 27-OHC, 7β-OHC, and 7-KC) were found elevated in AD brain and further exacerbate cell-damage by sustaining free-radical chain reactions [139–141] and insulin resistance [142]. Alterations of mitochondrial functions during brain insulin resistance also led to defects in synaptic plasticity mechanisms [143, 144]. Hence, brain insulin resistance, by favoring the imbalance in mitochondrial dynamics and functions within the brain, contribute to disturbances in neuronal apoptosis, as well as synaptic plasticity, cognitive decline, and cerebral degeneration.

7. Oxidative stress-induced damage in brain to proteins of the insulin signaling cascade

While a plethora of papers highlight the role for OS in favoring development of brain insulin resistance, whether increased ROS/RNS production also favor damage of proteins within the insulin signaling cascade is poorly explored. In our opinion, this represents an intriguing and novel aspect particularly in light of previous data from the Butterfield group showing OS-induced damage to proteins regulating cell metabolism in AD [25].

We identified two oxidatively modified proteins in AD brain or AD animal models highly relevant to insulin signaling: insulin degrading enzyme (IDE) [145–149]; and biliverdin reductase-A (BVR-A) [76, 150–154]. Moreover, both IDE and BVR-A were found to be dysregulated in T2DM/obesity peripheral tissues [155–160], thus suggesting their potential contribution to brain dysfunctions (Figure 3).

In this picture oxidative-induced damage to IDE and BVR-A might represent early alterations triggering the development of brain insulin resistance.

We also acknowledge that other proteins belonging to the insulin signalling pathway, including IRS1, PTEN and Akt, were found oxidatively impaired by HNE-adducts in *in vitro* models [161–163]. However, the above-mentioned studies were conducted in adipocytes [161] and hepatic cells [162]. For that reason, in the next sections we focus on proteins found to be oxidatively impaired within the brain.

7.1 Insulin degrading enzyme oxidation

Insulin-degrading enzyme (IDE) is a neutral Zn^{2+-}metallo-endopeptidase that is ubiquitously expressed in insulin-responsive and non-responsive cells [164]. IDE is evolutionarily ancient, with homologs present in phylogenetically diverse organisms of every kingdom [165]. As its name implies, IDE has a high affinity for insulin, but it can degrade a wide range of other peptide substrates, including glucagon, β-amyloid, and chemokine ligand 3 [164, 166]. IDE knockout mice are both glucose-intolerant and hyper-insulinemic, supporting the concept that IDE is important in the maintenance of normal blood glucose and insulin levels [167]. Human genetic studies have linked polymorphisms in the *IDE* gene to an increased risk for insulin resistance and T2DM [168–170]. Human genetic studies have also linked IDE to AD [171–173]. IDE hypofunction has been shown to contribute to the accumulation of Aβ plaques in animal models of AD [167]. In addition, a recent study from de la Monte and colleagues showed that IDE levels are altered both in mouse model of sporadic AD and in human AD brain suggesting that IDE plays a role in insulin deficiency and attendant insulin resistance in the early and intermediate stages of AD [174]. Consequently, factors that affect the activity of IDE could have significant impact on the progression of these diseases.

Indeed, a great interest in AD field toward IDE functions arose following the first identification of IDE as a physiologically relevant Aβ- degrading protease at multiple sites [175]. The original observation that IDE was able to hydrolyze Aβ in vitro [175] was extended by Selkoe and colleagues who demonstrated that a microglial cell line

secreted a metalloprotease immunologically identical to IDE, which was able to regulate extracellular levels of Aβ [176]. IDE also protects mitochondria against Aβ accumulation and dysfunction [177]. Since that time, IDE has been regarded as a significant contributor to Aβ degradation both *in vitro* and *in vivo*.

A role for IDE in favoring brain insulin resistance mostly rely on its ability to degrade Aβ. In fact, as reported by De Felice and colleagues, Aβ oligomers are able to bind to IR causing a major loss of IRs from neuronal dendrites and thereby reduce the activation of insulin signaling in neuronal cells [178], i.e., a mechanism leading to brain insulin resistance. Conversely, insulin prevents Aβ oligomers-induced loss of surface IRs, neuronal oxidative stress, and synapse deterioration [179]. The mechanism of insulin protection involves IR signaling–dependent downregulation of oligomer binding to neurons. Thus, the protective action of insulin in rescuing the inhibition of IRS1 and thus recovering the activation of the insulin signaling cascade in neurons likely derives from its ability to block oligomer binding to neurons [179]. Correspondingly, the finding that Aβ plaque size inversely correlates with IDE expression and activity [180, 181] suggests that IDE deficiency could mediate plaque buildup and possibly cognitive impairment in AD. In this picture, IDE activity would favor Aβ degradation, thus preventing both IR loss and development of brain insulin resistance (Figure 3).

Linking the above to OS, previous reports demonstrated that IDE can be oxidatively modified, resulting in reduced activity both in T2DM and AD [145–148]. Hersh and colleagues first reported that IDE was inactivated by reaction with 4-hydroxy-2-nonenal (HNE) with the concomitant formation of protein adducts and that oxidation increased its susceptibility to proteolysis [149]. Later, Cordes and colleagues described an additional mechanism for IDE inactivation driven by nitric oxide (NO). NO donors caused S-nitrosylation of IDE that led to diminished insulin and Aβ degrading activities of IDE *in vitro* (Figure 3). Insulin-degrading activity appeared more sensitive to NO inhibition than Aβ degrading activity [145]. Similar results were collected *in vivo* by showing that the activity of IDE was lowered in APP/PS1 mice (a model for AD), but not in mice lacking the inducible form of nitric oxide synthase (NOS2) [APP/PS1/NOS2(−/−) mice]. These data suggest that NOS2 upregulation impaired amyloid-β degradation through negative regulation of IDE activity and, as a consequence, loss of NOS2 activity would positively influence Aβ clearance by IDE [146].

Results collected in AD were further extended to T2DM/obesity by the group of Lipton and co-workers [147]. In an elegant paper these authors reported in human and rodent tissues that elevated glucose, as found in T2DM, and oligomeric Aβ peptide, which as noted above is thought to be a key mediator of AD pathogenesis, coordinately increased neuronal Ca^{2+} and NO in an NMDA receptor-dependent manner [147]. The increase in NO results in S-nitrosylation of IDE, thus inhibiting insulin and Aβ catabolism as well as hyperactivating mitochondrial machinery. Consequent elevation in Aβ levels and compromised mitochondrial bioenergetics resulted in dysfunctional synaptic plasticity and synapse loss in cortical and hippocampal neurons. The NMDA receptor antagonist memantine attenuated these effects [147]. Thus, this study suggested that redox-mediated

post-translational modification of IDE links Aβ and hyperglycemia to cognitive dysfunction in T2DM and AD [147] (Figure 3).

7.2 Biliverdin reductase-A (BVR-A) oxidation

The insulin signaling cascade contains several regulatory points, signal divergences, and crosstalk with other signaling pathways that represent critical nodes [182]; many steps are negatively regulated by phosphatases or inhibitory proteins, and the complexity of this signaling system is crucial for mediating the variety of insulin-related biological functions. Among them, the protein BVR-A emerged for its pleiotropic functions. BVR-A is mainly known for its canonical activity in the degradation pathway of heme, since BVR-A catalyzes the reduction of biliverdin (BV) to bilirubin (BR). However, previous studies *in vitro* showed that BVR-A arguably has a more diverse and expansive spectrum of functions because its numerous consensus regulatory motifs and its ability to fold into a protein–protein interactive structure [183]. Noteworthy, BVR-A is a unique serine/threonine/tyrosine (Ser/Thr/Tyr) kinase directly involved in the regulation of the insulin signaling [184, 185] at different levels. BVR-A is a direct target of the IR kinase activity, similar to IRS1. IR phosphorylates BVR-A on specific Tyr residues (Tyr198/228/291) and such phosphorylation is required for the activation of BVR-A kinase activity. In addition, as part of a regulatory loop, BVR-A phosphorylates IRS1 on inhibitory Ser residues (i.e. 307, 312, 616) to prevent IRS1 aberrant activation in response to IR [184] (Figure 1). In addition, BVR-A kinase activity is required for the activation of the extracellular signal-regulated kinases 1/2 (ERK1/2) [186]. Downstream from IRS1, BVR-A also functions as scaffold protein (Figure 1) favoring: (i) the PDK1-mediated activation of the aPKCζ [187], known to regulate either GLUT-4 translocation [188] or memory processes [189]; and (ii) the Akt-mediated inhibtion of GSK-3β [190]. Finally, BVR-A contains specific motifs in its sequence through which these motifs conceivably modulate IR kinase activity both negatively and positively [185].

Findings from animal models of obesity showed that loss of hepatic BVR-A is associated with altered glucose/insulin metabolism and increased fat accumulation [158]. Similarly, adipocyte-specific deletion of BVR-A caused increased expansion of visceral fat and adipocytes size, inflammation, reduced mitochondria number and hampered insulin signaling [157]. Evidence collected *in vitro* and animal models of metabolic disorders were strengthened by results from our group recently showing that reduced BVR-A levels were associated with the aberrant activation of insulin signaling, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD) and visceral adipose tissue inflammation in obese individuals [155, 156, 191].

During the past several years, we have focused much research on BVR-A especially in AD [76, 150–153, 192–197]. In addition, we found that reduced levels or impaired BVR-A activation contribute to the development of insulin resistance and metabolic alterations in the brain that are known to drive neurodegenerative processes [76, 124, 154, 190, 195, 197, 198].

The Butterfield group was the first to demonstrate that BVR-A activation was reduced in post-mortem MCI and AD brain because of increased nitration [higher 3-nitrotyrosine levels (3NT) on BVR-A] [150, 151, 153, 195]. In addition, increased BVR-A nitration was

associated with higher pIRS1 Ser307 levels in the same brain samples [67], thus suggesting that oxidatively induced damage of BVR-A likely contributes to the onset of brain insulin resistance in AD (Figure 3).

This hypothesis was further supported by data collected in a longitudinal study in which we found that the impairment of BVR-A is one of the earliest events observed during the development of brain insulin resistance in 3xTg-AD mice (a model to study AD) and that this phenomenon occurs before a consistent accumulation of Aβ and Tau as well as increased TNFα levels [76]. Of note, we proposed a role for OS in mediating BVR-A dysfunction: higher levels of OS markers paralleled the oxidative-induced damage at the expense of BVR-A, and both these events preceded the frank inhibition of IRS1 in the brain [76]. BVR-A oxidation reduced its kinase activity, which resulted first in the hyper-activation of IRS1 (in agreement with the regulatory role for BVR-A discussed above) and then in the inhibition of IRS1 mediated by the activation of inhibitory feedback mechanisms such as mTOR [76] (Figure 3).

The impairment of BVR-A also produces deleterious effects downstream from IRS1. Notwithstanding IRS1 hyper-activation, neither an increased activation of Akt nor an increased inhibition of GSK-3β were observed [190]. These data agree with the role for BVR-A in working as scaffold protein, favoring the PDK1-mediated activation of Akt as well as the Akt-mediated inhibition of GSK-3β in response to insulin [190, 199] (Figure 3). Therefore, OS-induced damage of BVR-A might turn-off the activation of insulin signaling, reducing its neuroprotective effects before a frank brain insulin resistance develops. These alterations produced detrimental effects on cognitive functions [198], while loss of BVR-A was found to impair long term potentiation (LTP), a key mechanism in learning, in cortical neurons [198].

As discussed above, brain insulin resistance has been proposed to have a role in the production and accumulation of Aβ in AD [66, 126, 127, 200]. Consequently, in a vicious cycle, increased Aβ oligomer generation further exacerbates brain insulin resistance through the down-regulation the of the IR, possibly because reduced IDE activity [179] (Figure 3). Within this picture, our group unraveled a novel mechanism linking BVR-A impairment, brain insulin resistance and increased Aβ production [154]. In particular, the impairment of BVR-A would favor the casein kinase I (CKI)-mediated phosphorylation of BACE1 and associated increased Aβ production along with the alteration of brain insulin signaling [154]. Therefore, these results support a role for BVR-A as molecular target whose dysfunction links brain insulin resistance with increased Aβ production in AD, which is associated with elevated oxidative stress [11].

Finally, increased 3-NT modifications of BVR-A observed both in human AD brain and in 3xTg-AD mice were found to be associated with mTOR hyper-activation [67, 76]. mTOR is a master regulator of autophagy [201, 202], and an hyper-activation of mTOR – which negatively regulates autophagy induction – along with the reduction of the autophagic flux was reported in AD [67, 203–205]. mTOR hyper-activation favors the accumulation of protein oxidative damage within the brain [79]. Moreover, mTOR hyper-activation is listed among the known feedback mechanisms responsible for IRS1 inhibition and

the development of insulin resistance also in AD [67, 203–206]. Among the pathways responsible for mTOR hyperactivation in AD, our group identified the impairment of BVR-A as a crucial event responsible for the disruption of the AMPK/mTOR axis resulting in mTOR hyper-activation in the brain [76, 198, 207] (Figure 3).

This aspect is of interest because AMPK is considered a key cellular energy sensor and it has a crucial role in the control of several processes ranging from lipid biosynthesis and catabolism to glucose uptake and antioxidant defense and regulation of insulin signaling [208]. AMPK is dysregulated in major metabolic disorders such as diabetes, obesity, as well as in neurodegenerative diseases [209, 210]. A dysregulation of the BVR-A/AMPK axis fostered by increased OS levels in the brain may therefore contribute to the development of brain insulin resistance either through mTOR hyper-activation or other pathways as discussed below (Figure 3).

8. AMPK is a central hub between metabolic defects and neurodegeneration

Epidemiological studies demonstrated that metabolic diseases, such as obesity, diabetes and hypercholesterolemia, are common risk factors for cognitive impairment and sporadic AD [211, 212]. As supported by PET imaging analysis of brains from AD and MCI subjects, and of populations at-risk of dementia, reduced glucose uptake and utilization is an early sign of neurodegeneration [11, 213]. In addition, the reduction of glucose utilization was shown to positively correlate with cognitive impairment [214]. AMPK is a metabolic serine/threonine protein kinase that serves as an “energy receptor” by coordinating cell metabolism and energy needs [215]. Short-term effects of AMPK activation can rapidly regulate energy metabolism, while long-term effects can regulate gene transcription [216].

Several lines of evidence have demonstrated that dys-regulated AMPK is involved in the onset and progression of AD, serving as neuronal metabolic sensor [210, 217–219]. Also, in T2DM patients, aberrant AMPK activity alters the metabolism of glucose and lipids and affects the levels blood glucose as well as the profile of blood lipids [215, 220]. As noted above, the core pathological feature of T2DM is insulin resistance that results in decreased insulin sensitivity and glucose utilization rate, thus reducing energy production and promoting cognitive decline [1, 44, 221]. AMPK is closely related to the development of insulin resistance, thereby playing an important role in the reduction of cognitive performances associated with the pathogenesis of AD. Therefore, AMPK appears to link energy metabolism to neurodegeneration, and this, in turn, suggests that energy deficiency is associated with altered synaptic transmission and memory impairment [210, 218].

AMPK exists as a heterotrimeric complex composed of α-catalytic subunit and β- and γ-regulatory subunits. The α-, β-, and γ-subunits can also be found in different isoforms: γ1, γ2, or γ3 isoform for γ-subunit; β1 or β2 isoform for β-subunit; and α1 or α2 isoform for α-subunit [222, 223]. AMPK functions as an intracellular sensor of energy when activated in response to stress conditions, such as low glucose, hypoxia and ischemia, each of which depletes cellular ATP supplies and yields an increased AMP/ATP concentration ratio [224].

Regulation of AMPK activity involves both direct allosteric activation by AMP and reversible phosphorylation of AMPKα subunit on Thr^{172} by upstream kinases [222]. Phosphorylation (of Thr^{172}) is quantitatively much more significant than the allosteric activation because it causes at least 50- to 100-fold increase in AMPK activation [210]. However, the activation of AMPK needs two conditions, including the γ-subunit conformational change, to expose the active phosphorylation site on the α-subunit and the subsequent phosphorylation of AMPK on its activating loop by upstream kinases [219]. The major mechanisms that lead to AMPK activation, through the phosphorylation of Thr^{172} are catalyzed by LKB1 complex (LKB1/STRAD/MO25) in response to the increased AMP/ATP ratio, and by calmodulin-dependent protein kinase kinase-beta (CaMKKβ) in response to elevated Ca^{2+} levels. Conversely, Thr^{172} is dephosphorylated by protein phosphatase-2C (PP2C) to turn active AMPK into the inactive form [215, 218, 223, 225]. The major function of AMPK is to switch on energy-producing processes and to switch off energy-consuming functions. Thus, AMPK promotes glucose uptake and glycolysis, fatty acid oxidation, and mitochondrial biogenesis, which ultimately increase ATP production. On the other hand, AMPK inhibits anabolic processes such as protein synthesis and decreases ATP consumption.

AMPK signaling also has a crucial role in regulating food intake in hypothalamic neurons [226]. AMPK negatively regulates several proteins central to ATP-consuming processes such as the transducer of regulated CREB activity 2 (TORC2), glycogen synthase, sterol regulatory element-binding proteins (SREBP), and tuberous sclerosis protein 2 (TSC2). Thus, AMPK activation results in the down-regulation or inhibition of gluconeogenesis, glycogen, lipid, and protein synthesis [218, 219].

With regard to the interaction between AMPK and insulin signaling, insulin resistance leads to repression of general AMPK activity through the over-activation of AKT. Further, by inhibiting AMPK activity, Aβ oligomers can decrease the surface levels of glucose transporters (GLUT) in hippocampal neurons, which results in insulin resistance [227]. In turn, insulin resistance can increase amyloidosis via mechanisms involved in the repression of insulin-PI3KAKT signaling [228], resulting in the upregulation of GSK3β activity. In agreement with the above, increased AMPK activation induces IRS phosphorylation at tyrosine residues, thereby promoting insulin signaling activities by inhibiting GSK3β [229, 230]. Furthermore, AMPK activation can promote the expression of GLUT4 or GLUT1, increasing the rate of glucose utilization and leading to the production of large amounts of ATP that improve neuronal activity and homeostasis [215].

As an energy sensor regulating all aspects of cellular functions, AMPK also has numerous downstream targets participating in biosynthetic pathways. Of particular interest is that AMPK can regulate protein homeostasis (synthesis/degradation rate), which is indispensable for long-lasting forms of synaptic plasticity and memory [219, 231].

8.1 Role of AMPK in Aβ and p-tau development

Given the participation of AMPK in the regulation of several mechanisms associated with memory and cognition, it is not surprising that abnormal AMPK activity has been reported in postmortem AD patients, as well as, in AD mouse models [215–217]. Intriguingly,

AMPK dysregulation has been strongly associated with AD progression, however its role is still controversial, especially with regard to Aβ accumulation and tau phosphorylation. Studies reporting the positive or negative effects of AMPK on Aβ or tau demonstrated diverse mechanisms of action [226]. However, although there are conflicting results, there is no disagreement about the involvement of AMPK in AD pathogenesis. Several reports demonstrated that the activation of AMPK reduces the β-cleavage of APP in cultured rat cortical neurons, while knockout of AMPKα2 increases Aβ production [217, 232]. In agreement with these findings, the stimulation of AMPK by leptin was demonstrated to reduce Aβ deposition, whereas inhibitors of AMPK block the effects of leptin [233, 234]. This observation was corroborated by epidemiological studies, which showed lower leptin levels in AD patients compared to those in healthy individuals [226]. In addition, the direct stimulation of AMPK with 5-amino-imidazole-4-carboxamide ribonucleoside (AICAR), an AMPK agonist, replicated the effect of leptin and decreased Aβ production, whereas compound C, an AMPK inhibitor, increased Aβ production [235]. The pharmacological activation of AMPK by resveratrol in APP-transfected cells (APP-HEK293 and APP-N2a) or quercetin in aged mouse brain lowered the extracellular concentration of Aβ by reducing the expression of BACE1 and the formation of Aβ. Furthermore, metformin was shown to interact with BACE1 and AMPK; however, studies concerning the reduction of Aβ have been conflicting so far [236, 237]. Other studies, employing different AMPK agonist molecules, reported that the activation of AMPK decreases the expression of BACE1 at the transcription and translation levels [237]. Among the molecular mechanisms for reduction of BACE1 expression, a role for the attenuation of translation initiation factor eIF2α upon AMPK activation was proposed [238]. Moreover, the activation of AMPK is known to activate autophagy, and recent studies showed that upregulation of autophagy can reduce BACE1, therefore partially explaining why the levels of BACE1 were found to be reduced upon AMPK activation [215–217, 239].

Overall, the above-mentioned findings suggest that AMPK activation can moderate Aβ production by decreasing BACE1 expression; however, another reported mechanism by which AMPK control amyloidogenesis is by regulating the metabolism of cholesterol and sphingolipid [226]. AMPK regulates cholesterol and sphingolipid biosynthesis by controlling the gene expression and activity of associated enzymes. Recent pieces of evidence also show that reduction of cholesterol and sphingolipids decreases the generation of Aβ [240, 241]. However, the exact mechanisms linking AMPK activation with reduced Aβ production through sphingolipids and cholesterol metabolism is still under investigation.

In contrast, other studies supported the notion that the activation of AMPK can lead to the biogenesis of Aβ peptides and to the development of AD, of course being detrimental for the brain. As an example, metformin was shown to increase the biogenesis of Aβ through the activation of AMPK [242, 243]. In agreement, a population-based large-scale case-control study showed that the treatment of T2DM patients with metformin was associated with a slightly higher risk of AD development [244]. Additional studies demonstrated that metformin increased the generation of Aβ by different mechanisms involving the accumulation of autophagosomes and the resultant increase of β- and γ-secretases [245], as well as, the increase expression of BACE1 and APP [246]. Therefore, there is consistent

evidence that the activation of AMPK with metformin might play a negative role in the pathogenesis of AD.

The role of AMPK in AD also is debatable with regard to tau phosphorylation [216]. Abnormally increased p-AMPK levels were found in the cytoplasm of cortical neurons in multiple tauopathies including AD. p-AMPK and p-tau protein demonstrated strong co-localization in pre-tangle-and- tangle-bearing neurons in most brain regions affected by tau pathology in AD patients [247]. Tau pathology is closely associated with mitochondrial failure due to its negative effects on mitochondrial transport, mitochondrial fission and fusion, and mitophagy [248]. Indeed, it has been proposed, that pathological forms of tau could disrupt axonal transport and cause synaptic damage by the increase of the pausing frequency of mitochondria movement the reduction of anterograde movement of mitochondrial [249]. Furthermore, tau play a significant role in the impairment of mitochondrial fission/fusion dynamics through the increase of the mitochondrial fission proteins, such as Drp1, and the decrease of fusion protein including OPA-1, Mfn1/2 [250]. Several *in vitro* studies demonstrated that AMPK is a tau kinase, which can phosphorylate tau protein at multiple sites within the microtubule binding domain and the flanking region [216, 251]. On the other hand, AMPK also may be involved in the reduction of tau levels and tau phosphorylation through various downstream mechanisms [215, 218]. For example, mounting evidence suggests that AMPK, by increasing the availability of NAD^+, enhances SIRT1, a class III protein deacetylase, leading to decreased acetylation and increased degradation of tau protein [217]. Indeed, it was demonstrated that increased acetylation of tau inhibits the ubiquitinylation and the degradation processes of tau protein [252]. A further mechanism by which AMPK activation led to reduced tau phosphorylation is by activation of PP2A [253]. PP2A is one of the main dephosphorylating enzymes involved in the regulation of tau PTMs. Several studies have shown that the level and activity of PP2A are lowered in the brain from AD patients obtained by autopsy and in animal models of the disease, showing strong involvement of decreased PP2A in the generation of tauopathy [254, 255]. Furthermore, in T2DM animal models the significant increase of tau phosphorylation was associated with AMPK impairment as an effect of PP2A inhibition, decreased SIRT 1 activity, and GSK3β overactivity [256, 257]. Taken together, the activation of AMPK seems to interfere with tau phosphorylation by different mechanisms that include the decreased the activity of GSK3β, the increased the activity of PP2A and the increased proteasomal degradation of tau as an effect of SIRT1 activation [226]. However, the overall net effect of AMPK activation on tau phosphorylation remains to be fully elucidated. Indeed, as described above, AMPK has a direct negative effect on tauopathy and has an indirect protective effect through its downstream mediators. In addition, the indirect positive effects of AMPK are complex as they include the bidirectional regulation of different regulators of tau phosphorylation.

Therefore, up to the present, whether activation of AMPK activity would be either beneficial or detrimental for Aβ deposition and tau phosphorylation remains controversial.

8.2 AMPK regulates brain proteostasis and redox balance

In addition to participating in the regulation of insulin resistance, and of Aβ and p-tau formation, AMPK plays a crucial role in preventing AD by promoting autophagy and improving mitochondrial function [216, 217]. Reduced autophagy is observed during the development of AD [258]. The mammalian target of rapamycin complex 1 (mTORC1) inhibits the occurrence of autophagy, thus favoring the build-up of toxic proteins and the aggregation of Aβ and the formation of NFTs [206, 259]. mTORC1 is activated by insulin, growth factors and nutrients, and this complex participates in insulin signaling resulting in increased translation. Insulin induces mTORC1 activity by inhibiting the tumor suppressor complex (TSC1/TSC2), which is an endogenous mTORC1 repressor [260]. AMPK is widely recognized as an mTOR antagonist and prevents the mTORC1 from phosphorylating its substrates, thus affecting autophagy [215]. Indeed, AMPK promotes autophagy by directly activating Ulk1 through phosphorylation of Ser 317 and Ser 777, while mTOR activity prevents Ulk1 activation by phosphorylating Ulk1 Ser 757 and disrupting the interaction between Ulk1 and AMPK. Further, AMPK indirectly inhibits mTORC1 by the activation of TSC1 and TSC2 through the phosphorylation of both Thr^{1227} and Ser^{1345} on TSC2 (Figure 4). Moreover, AMPK is able to inhibit mTORC1 activity by directly phosphorylating RAPTOR, a component of the complex [243]. Recently, the activation of AMPK was shown to be important not only in autophagosome formation but also in autophagosome clearance and can improve the overall autophagic degradation of aberrant proteins [226]. Several studies have shown that AMPK is one of the major positive regulators of autophagy demonstrating that enhanced autophagy was able to promote the clearance of Aβ [261, 262]. Further evidence demonstrated that the increase in cytosolic Ca^{2+} can induce autophagy by inhibition of mTOR through the CaMKKβ-mediated activation of AMPK [263, 264].

Mitochondrial defects are also strong contributors to synaptic deficits, an early pathophysiological feature of AD [216]. Peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α) is a member of the transcription coactivator family, and it is the initiator of mitochondrial biosynthesis. Several studies indicated that the levels of PGC-1α are decreased in AD patients and low levels of PGC-1α can lead to mitochondrial dysfunction and oxidative stress [265, 266]. Thus, the correct regulation of PGC-1α may represent an important step for the maintenance of cognitive function in AD [267]. In agreement with the above discussion, the activation of AMPK promotes mitochondrial biogenesis, mitochondrial quality control and the regulation of mitochondrial shape through the phosphorylation of PGC-1α on Thr^{177} and Ser^{538} sites, which lead to its increased activity [268]. Upon activation, PGC-1α is then translocated into the nucleus and interacts with several transcription factors, including the nuclear factor erythroid 2-related factor 1 and 2 (Nrf1 and Nrf2) [269]. This interaction induces a series of mitochondrial protein gene sequences encoded by nuclear genes [270]. Moreover, PGC-1α is also activated by AMPK-driven deacetylation of SIRT1, thus promoting mitochondrial biogenesis [271].

The control of mitochondrial function and biogenesis exerted by AMPK also is strongly related with the regulation of redox homeostasis. As noted above, the main source of ROS is the electron transport chain (ETC) at the mitochondrial inner membrane. ROS generated by mitochondria can increase BACE1 activity and consequently promote amyloidogenic

APP processing and Aβ overproduction [216]. Therefore, the regulation of ROS production might be crucial for protection against development of AD. Activation of AMPK can directly halt ROS overproduction via increasing the regulation of mitochondrial efficiency but also increase antioxidant protection through the activation of PGC-1α [271]. Therefore, AMPK functions as a redox-sensitive protein since it can be activated in response to excess ROS production, thereby coupling cellular ROS levels to mitochondrial metabolic homeostasis [272, 273]. Accordingly, cell lines lacking AMPKα expression displayed higher basal levels of mitochondrial ROS and, consistent with this finding, AMPKα knockout cells also rapidly underwent cell-death as a consequence of increased oxidative stress [273]. Different mechanisms are reported for the antioxidant function of AMPK. AMPK modulates the activity of several downstream proteins and processes involved in the redox balance including the enhancement expression of antioxidants, the activation of antioxidant enzymes, the decrease of ROS production and the stimulation of autophagic clearance [210, 215, 218]. Treatments with an AMPK agonist decreased intracellular and mitochondrial ROS burden, inhibited lipid peroxidation, and improved antioxidant contents by increasing the activity of endogenous antioxidant enzymes [274, 275]. In parallel, the administration of antioxidants was demonstrated to reduce the basal activation of AMPK [226].

Furthermore, as mentioned already, AMPK is an upstream activator of Nrf2, a master regulator of antioxidant gene programs [276, 277]. Once activated, Nrf2 translocates to the nucleus where it binds with the antioxidant response element and stimulates the expression of different antioxidant proteins such as heme oxygenase-1, NADPH quinone oxidoreductase-1, and Mn superoxide dismutase [278]. Nrf2 is reportedly reduced in AD human brain and in mouse models of the disease [279, 280]. Several *in vivo* and *in vitro* studies showed that the neuroprotective effect of AMPK activators was reversed by genetic deletion of both AMPK and/or Nrf2 genes [281, 282]. Therefore, the AMPK/Nrf2 pathway is one of the main antioxidant mechanisms of AMPK activation. In addition, PGC-1α, once activated by AMPK, translocates to the nucleus, and stimulates the expression of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase-1 (GPX1) enzymes [283, 284]. The activation of AMPK enhances the expression of SIRT3, a NAD^+ dependent protein deacetylase highly localized in the mitochondria [226]. SIRT3 in turn deacetylates SOD2 and decreases mitochondrial ROS [1, 220]. Thus, the induction of the AMPK-SIRT3-SOD2 pathway activates antioxidants already synthesized in the cell. In contrast, a recent study suggested that increased oxidative stress represents the underlaying mechanism leading to the concomitant activation and uncoupling of AMPK and mTOR, as observed in AD brain [285]. The induction of autophagy also is involved in the regulation of the redox status of the brain by degrading oxidized proteins and by activating antioxidant responses driven by the autophagy receptor p62/SQSTM1 [286–289]. Finally, AMPK also phosphorylates and decreases the transcription factor sterol regulatory element-binding protein-1c (SREBP-1c), thereby reducing the expression of lipogenic genes [210].

8.3 AMPK controls protein O-GlcNacylation

O-linked N-acetylglucosamine (O-GlcNAc) is a sugar post-translational modification participating in a diverse range of cell functions. A wide scope of cellular processes

is controlled and fine-tuned by O-GlcNAc, including apoptosis, mitochondrial function, proliferation, and gene transcription [290–292]. The rate of protein O-GlcNAcylation is mediated by two enzymes: O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA), and their alteration is involved in the disruption of O-GlcNAc cycling. O-GlcNAcylation is dependent on the intracellular concentration of UDP-GlcNAc from the hexosamine biosynthetic pathway (HBP) [293]. The HBP integrates the metabolic information of nutrients, including carbohydrates, amino acids, fatty acids, and nucleic acids, in the process of UPD-GlcNAc synthesis [294]. Further, HBP regulates energy homeostasis by controlling the production of both insulin and leptin [295]. O-GlcNAcylation is tightly coupled to insulin resistance since hyperglycemia- or hyperlipidemia-induced insulin resistance is closely related to altered HBP flux, and, in turn, the subsequent aberrant O-GlcNAcylation modifies insulin signaling, glucose uptake, gluconeogenesis, glycogen, and fatty acid synthesis [292, 296–298].

In this scenario, O-GlcNAcylation represents a key mechanism linking nutrient overload and insulin resistance, and its dysregulation might promote the transition from metabolic defects to chronic diseases such as T2DM and AD [299]. Indeed, obesity and peripheral hyperglycemia, by promoting insulin resistance and hypoglycemia in the brain, led to decreased O-GlcNAcylation of APP and Tau and to increased production of toxic Aβ and Tau aggregates, hallmarks of AD [290, 300]. HBP flux regulates multiple steps of the insulin signaling pathway and, in particular, IRS-1 has multiple O-GlcNAcylation sites, and its O-GlcNAcylation negatively correlates with changes in phosphorylation, which are a necessary in activating downstream pathways for glucose uptake [294, 296].

Investigations into the individual nutrient-sensitivities of the HBP, AMPK, and mTOR pathways revealed a complex regulatory dynamic, by which their unique responses to macromolecule levels coordinate cell behavior. Importantly, the crosstalk between these pathways fine-tunes the cellular response to nutrients (Figure 4). By the action of AMPK, GFAT1, the first rate-limiting enzyme of the HBP, undergoes negative regulation through increased phosphorylation on Ser^{243} [301, 302]. Studies on HFD mice demonstrated the concomitant occurrence of brain insulin resistance and reduced protein O-GlcNAcylation that converge in the development of AD markers [295]. Indeed, the brain from HFD mice exhibited increased inhibition of IRS-1 along with increased AMPK activation, which exerted a negative regulation on GFAT1 activity, by the direct phosphorylation of the Ser^{243} inhibitory residue, thus resulting in reduced protein O-GlcNacylation and increased phosphorylation of APP and tau [290, 295]. Different studies also showed that AMPK itself was O-GlcNAcylated on several residues, allowing one to posit further feedback mechanisms between these systems [299]. Thus, experimental evidence supports a regulatory role for OGT in controlling AMPK activity. On the other hand, AMPK phosphorylation of OGT on Thr^{444} increases OGT nuclear localization, increases nuclear O-GlcNAcylation and increases histone H3K9 acetylation, while O-GlcNAcylation of the H2B histone is lower, suggesting AMPK as a regulator of OGT activity and of O-GlcNAc mediated epigenetic modifications [299]. In addition, the rescue of O-GlcNAcylation brain levels was shown to stimulate autophagosome maturation and lysosomal degradation, suggesting a crosstalk between OGT/OGA cycling and autophagy that conceivably also might involve the AMPK/mTOR signaling [290].

9. Conclusions

AD and T2DM are two highly prevalent conditions affecting people worldwide. Clearly, a better understanding of the molecular bases of both conditions, and especially their intersection of molecular processes, we posit, will identify important therapeutic targets for both conditions.

It is toward this end that this review paper presents major underlying molecular processes in and the interplay among oxidative stress, glucose dysmetabolism, and the key protein AMPK in AD. Oxidative stress and glucose dysmetabolism are inextricably linked in the brain of AD individuals [11]. Insulin signaling, specifically the development of insulin resistance, also find commonality in both the role of oxidative stress and their origins and key molecular and clinically relevant characteristics of T2DM and AD.

Not only is oxidative stress involved in driving development of clinical and pathological aspects of diabetes and AD, but, in a vicious cycle, pathological aspects in T2DM and AD can lead to oxidative stress [11]. Insulin resistance results when the information inherent in the binding of insulin to the plasma membrane-resident insulin receptor cannot be transduced to intracellular biochemical changes (often phosphorylation of important cellular proteins). The IRS1 protein is intimately involved in insulin signaling mechanisms as we outline above. This protein is regulated by several processes, two of which are BVR-A and secondary to mTORC1 activation [67, 206, 207]. The latter leads to resultant phosphorylation of p70S6K and subsequent inhibition of IRS1 [206].

In the case of AD, sources of oxidative stress are numerous, with two of the most relevant ones being mitochondrial dysfunction [77, 103] and Aβ42 oligomer-associated lipid peroxidation and its downstream sequela of HNE modification of glucose metabolic proteins, ion-motive ATPases, intracellular Ca^{2+} accumulation, synaptic dysfunction, and neuronal death [11]. In the case of mitochondria, significant superoxide free radical leak from Complex I of the electron transport chain immediately is attacked by MnSOD in the matrix to produce H_2O_2. The latter compound, due to its *trans*-configuration, has a zero dipole moment and is highly soluble in the hydrophobic core of the mitochondrial lipid bilayer. Any adventitious reduced Fe^{2+} or Cu^{+} would immediately react with this H_2O_2 to produce $^{\cdot}OH$ radical which would wreak havoc on the mitochondria [11, 303]. In the case of lipid-resident Aβ42 oligomer-associated lipid peroxidation, much is now understood on how lipid peroxidation ensues [11]. A major product of lipid peroxidation, HNE is highly reactive and neurotoxic [303]. Brain-resident HNE-bound proteins are significantly elevated in AD and T2DM, meaning that key metabolic, regulatory, and structural proteins have altered structure and diminished function [303–311].

Insulin signaling is fundamental to metabolic pathways needed for processes related to learning and memory [1]. In both AD and T2DM, insulin signaling is disrupted due to insulin resistance [66, 67, 81]. Craft and co-workers demonstrated that intranasal insulin delivery directly to brain (which precluded peripheral effects of elevated insulin) helped individuals with MCI and AD to improve cognition [49]. This same group demonstrated that dose level, gender, and ApoE allele status had complex yielded complex relationships

to cognition following intranasal insulin treatment [312]. More research is required to understand the molecular bases for these differences following intranasal insulin.

In addition to the above, other conclusions based on this review article are:

- Hydrogen peroxide, in addition to being an important reactive oxygen species, is involved in the activation of the IR in neurons [89].
- Oxidative stress is correlated to loss of synapses in AD and therefore in cognitive loss [100–104].
- Insulin degrading enzyme normally cleaves Aβ, rendering it non-neurotoxic, but in brain of AD and T2DM persons and animal models thereof IDE is oxidatively modified by HNE [145–148], leading to increased levels of neurotoxic Aβ and insulin resistance decreased function of IDE in a destructive cycle. That is, more Aβ leads to more lipid peroxidation with consequent synaptic loss and neuronal death with consequent loss of cognition, a hallmark clinical characteristic of AD.
- Defects in glucose metabolism are associated with insulin resistance in AD and MCI brains [11, 57, 80, 122] and important in the conversion of Down syndrome individuals to persons with Down syndrome and AD-like neuropathology and dementia [11, 128].
- Biliverdin reductase-A and AMP-activated protein kinase are critical for the associations among obesity, T2DM, and development of AD. Moreover, AMPK is a central locus between metabolic defects and neurodegeneration [191, 210, 217–219].

Alzheimer disease is a devastating dementing disorder; T2DM and insulin resistance are significant risk factors for development of AD. The current review provides evidence of some of the underlying molecular processes by which this association exists and points to potential therapeutic targets to slow or, ideally, halt progression of AD. We predict that expanded research directed toward these underlying Aβ-associated dysfunctional metabolic mechanisms will ensue as the number of persons worldwide at risk of developing AD is ballooning. We trust that this review paper contributes to this effort.

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List of Abbreviations

Aβ	β-amyloid protein
AD	Alzheimer disease
AGEs	advanced glycation end products
AMPK	AMP-activated protein kinase
APP	amyloid precursor protein

ATP	Adenosine triphosphate
AT	adipose tissue
Akt	protein kinase B
BVR-A	biliverdin reductase A
BBB	blood brain barrier
ER stress	endoplasmic reticulum stress
ERK1/2	extracellular signal-regulated kinase 1/2
GLUTs	glucose transporters
GSK3β	Glycogen synthase kinase 3 beta
HNE	4-hydroxy-2-nonenals
IDE	insulin degrading enzyme
IRS1	insulin receptor substrate1
IR	insulin receptor
IKkB	Inhibitor of nuclear factor kappa B kinase subunit neta
JNK	c-Jun N-terminal kinase
LTP	long term potentiation
MAPK	mitogen-activated protein kinase
MEK	mitogen-activated protein kinase kinase
MCI	mild cognitive impairment
mTOR	mammalian target of rapamycin
NFTs	neurofibrillary tangles
NMDA receptor	N-methyl-D-aspartate receptor
Nrf2	nuclear factor erythroid 2–related factor 2
O-GlcNAc	O-linked N-acetylglucosamine
OGA	O-GlcNAcase
OGT	O-GlcNAc transferase
OXPHOS	oxidative phosphorylation
OS	oxidative stress
PDK1	phosphoinositide-dependent kinase 1

PGC-1α	Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha
PKCζ	protein kinase C zeta
PPA2	inorganic pyrophosphatase 2
PTEN	phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase
PI3K	Phosphoinositide 3-kinases
PKR	protein kinase R
PTP1B	protein tyrosine phosphatase 1B
3-NT	3 -nitro-tyrosine
ROS	reactive oxygen species
RNS	reactive nitrogen species
SOD	superoxide dismutase
T2DM	type 2 diabetes mellitus
TNF- α	tumor necrosis factor alpha

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Highlights

- Defects in energy metabolism are common features for T2DM and AD
- Systemic insulin resistance is a risk factor for neurodegeneration
- Neurodegeneration is associated with brain insulin resistance and oxidative stress
- Oxidative stress contributes to brain insulin resistance by damaging BVR-A and IDE
- AMPK dampens oxidative stress levels, thus regulating brain redox homeostasis

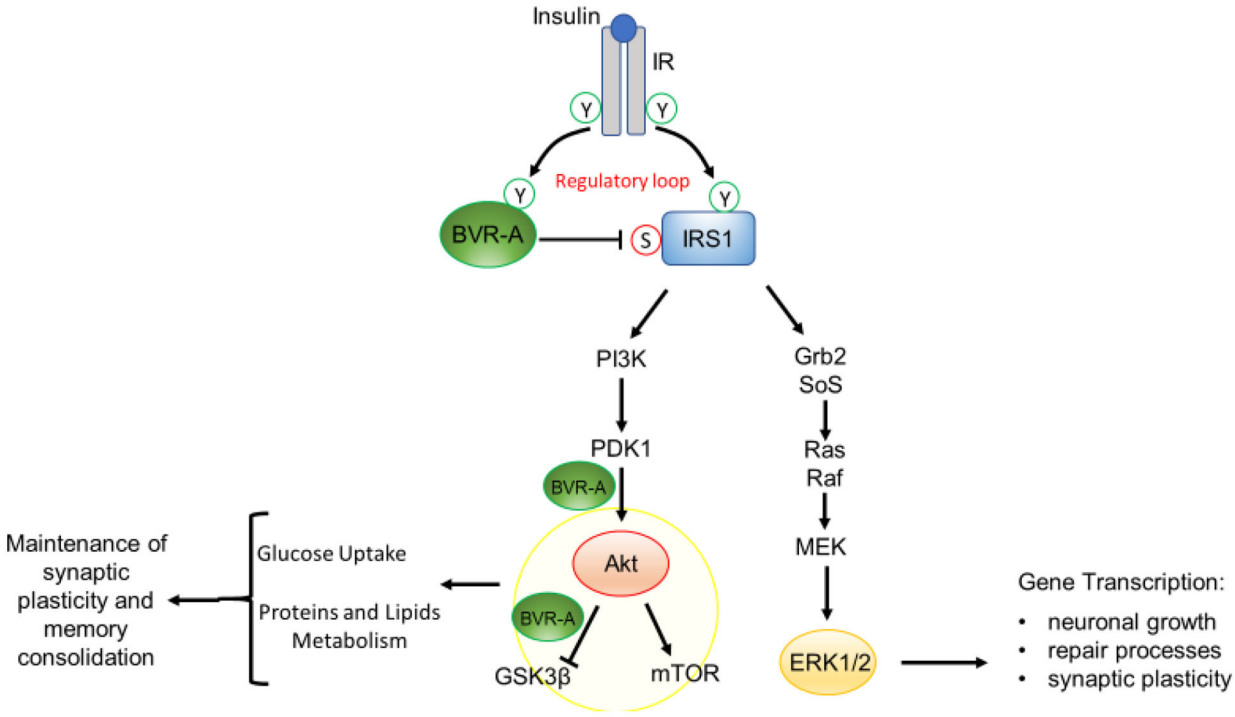

Figure 1. Schematic representation of insulin signaling.

Under physiological conditions, the activation of insulin signaling requires the binding of insulin to the insulin receptor (IR), which auto-phosphorylates on Tyr residues (Y, e.g., Tyr1158/1162/1163) and promotes the receptor tyrosine kinase-mediated phosphorylation of its substrate (IRS1) on specific Tyr residues (e.g., 632). In parallel, IR phosphorylates BVR-A on specific Tyr residues and activates BVR-A to function as Ser/Thr/Tyr kinase. Then, as part of a regulatory loop, BVR-A phosphorylates IRS1 on inhibitory Ser residues (S, e.g., Ser307/312/616) to avoid IRS1 aberrant activation in response to IR. Once activated, IRS1 works as a scaffold protein, driving the activation of the two main arms of the insulin signaling: (1) the Ras/Raf/MAPK pathway (ERK1/2) mainly involved in gene transcription; and (2) the PI3K/Akt axis that is critical for glucose uptake as well as for protein and lipid metabolism. Moreover, Akt promotes the phosphorylation of several targets, among which are: (1) GSK3β (on Ser9, inhibitory site), which has a role in energy production; and (2) mTOR (on Ser2448, activating site), which regulates protein synthesis and autophagy. Within this axis, BVR-A works as scaffold protein facilitating the PDK1-mediated activation of Akt and the Akt-mediated inhibition of GSK3β. Arrows represent stimulation; lines represent inhibition. See text for more details.

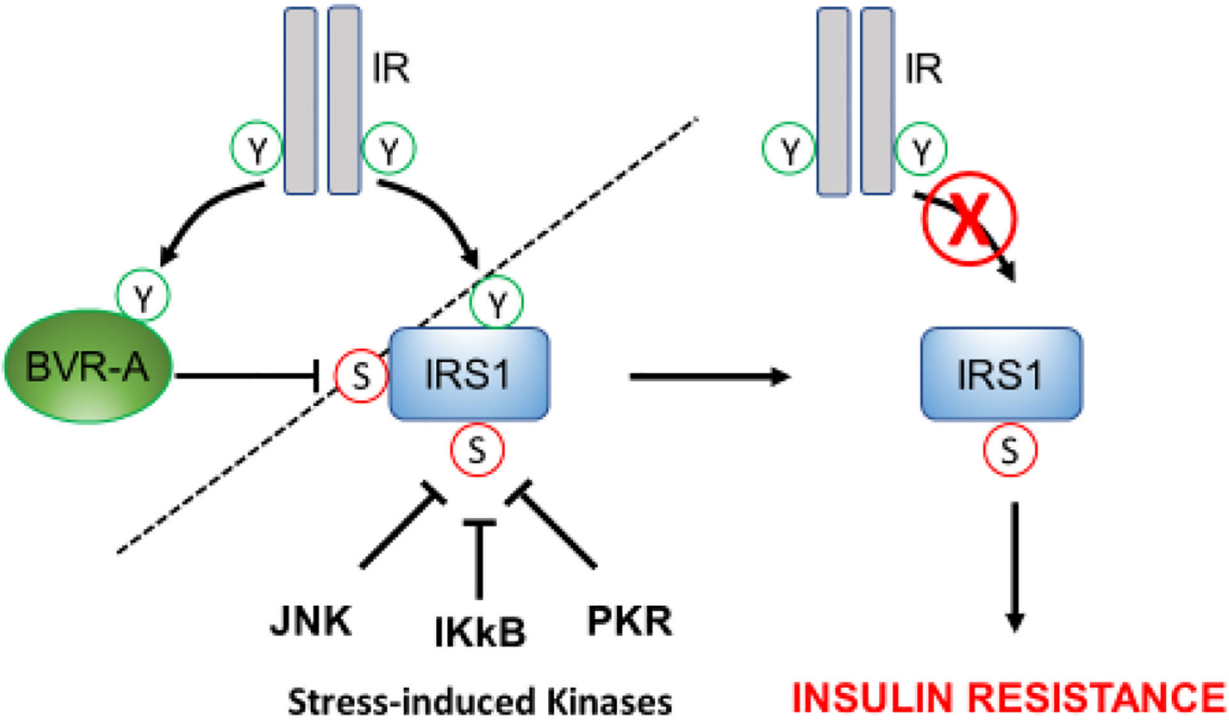

Figure 2. Classical mechanisms favoring brain insulin resistance development.

The brain insulin resistance phenomenon is characterized by key events such as reduced IR protein levels and/or increased IRS1 inhibitory phosphorylation levels (e.g., Ser307, Ser636), that are responsible for the uncoupling between IR and IRS1. As result, despite insulin binding to IR, IR-mediated activation of IRS1 does not occur. As a consequence, pathways downstream from IRS1 are not activated. Within this scenario, the inhibitory phosphorylation of IRS1is mediated by the aberrant activation of stress-induced kinases (i.e., JNK, IKK, PKR). Arrows represent stimulation; lines represent inhibition. See text for more details.

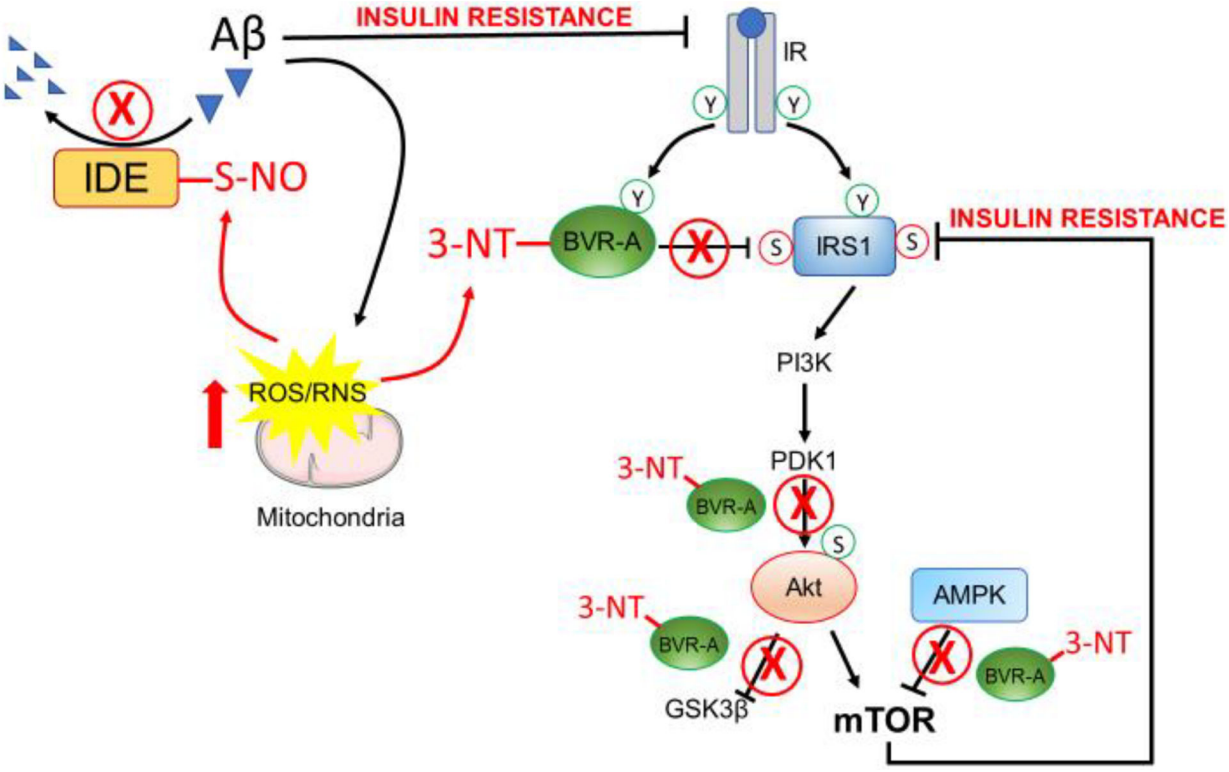

Figure 3. Oxidative stress-induced damage of IDE and BVR-A is associated with development of brain insulin resistance.

Mitochondria impairment results in increased levels of ROS/RNS that are able to damage proteins and lipids within cells. In particular, increased 3-NT modifications of BVR-A occur in AD brain and are responsible for reduced BVR-A activation and scaffold protein function. Such events result in the hyper-activation of IRS1 upstream in the pathway and in reduced activation of Akt downstream from IRS1. Moreover, the oxidative modification of BVR-A results in reduced ability for BVR-A to favor the AMPK-mediated inhibition of mTOR. As consequence, the hyper-activation of mTOR occurs and is responsible for the inhibition of IRS1 and thus the development of brain insulin resistance. Likewise, ROS/RNS elevation leads to the nitrosylation and consequent inhibition of IDE causing this enzyme not to contribute to Aβ degradation. In turn, increased Aβ levels lead to IR downregulation thereby reducing the pool of IR available at the plasma membrane to bind insulin. In parallel, increased Aβ levels further contribute to mitochondrial damage and increased ROS/RNS production. Arrows represent stimulation; lines represent inhibition. See text for more details.

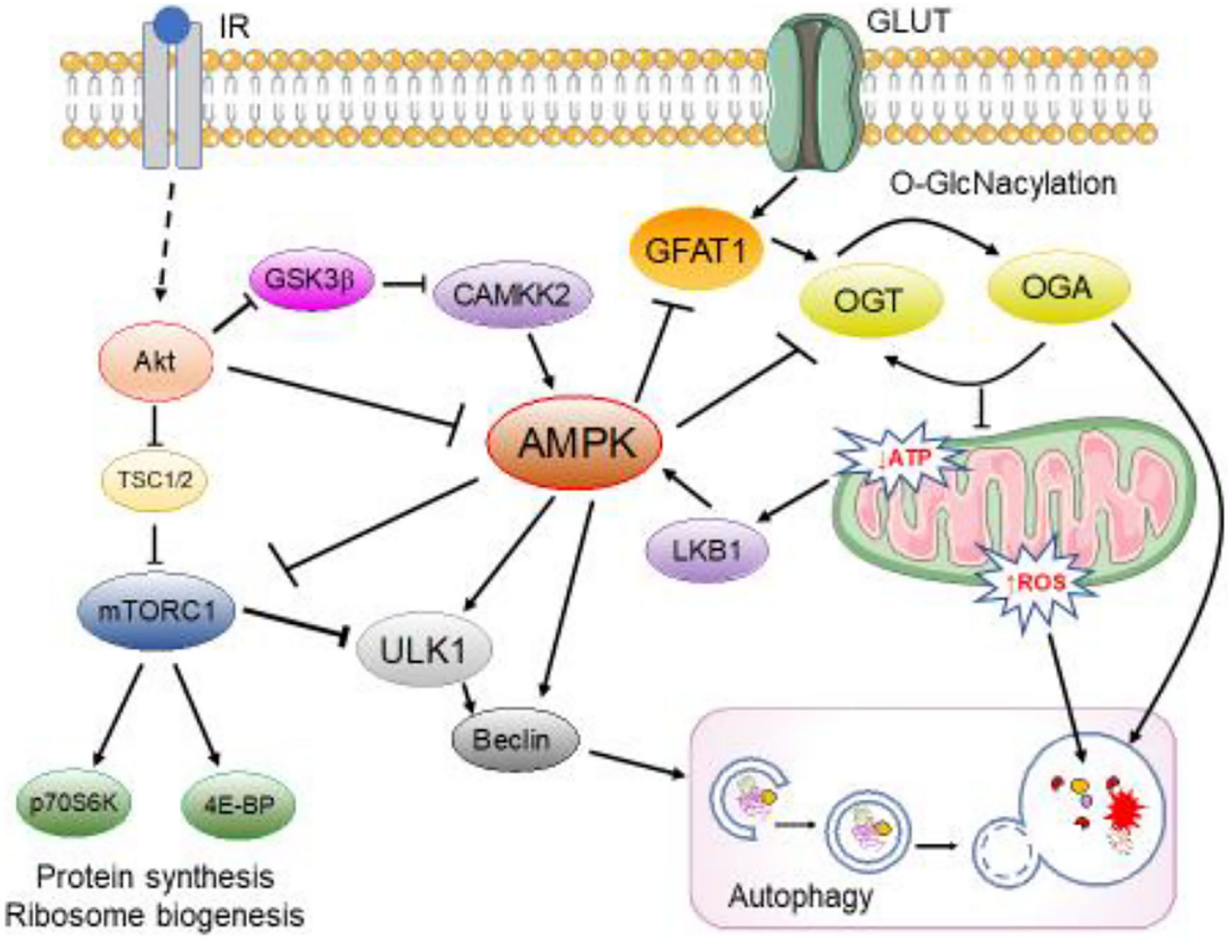

Figure 4: Schematic representation of the "metabolic" regulations exerted by AMPK.

AMPK is activated by the LKB1 complex in response to the increase in the AMP/ATP ratio and by CaMKKβ in response to elevated Ca^{2+} levels, while insulin resistance leads to repression of general AMPK activity through the over-activation of Akt. AMPK promotes autophagy by directly activating Ulk1 through phosphorylation of Ser 317 and Ser 777, while mTOR activity prevents Ulk1 activation by phosphorylating Ulk1 Ser 757 and disrupting the interaction between Ulk1 and AMPK. Further, increased AMPK negatively regulates protein O-GlcNacylation by inhibiting GFAT1 and by regulating OGT localization. Arrows represent stimulation; lines represent inhibition. See text for more details.