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Review

Insulin resistance in Alzheimer disease: Is heme oxygenase-1 an Achille's heel?

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ABSTRACT

Insulin resistance, clinically defined as the inability of insulin to increase glucose uptake and utilization, has been found to be associated with the progression of Alzheimer disease (AD). Indeed, postmortem AD brain shows all the signs of insulin resistance including: (i) reduced brain insulin receptor (IR) sensitivity, (ii) hypophosphorylation of the insulin receptor and downstream second messengers such as IRS-1, and (iii) attenuated insulin and insulin growth factor (IGF)-1 receptor expression. However, the exact mechanisms driving insulin resistance have not been completely elucidated. Quite recently, the levels of the peripheral inducible isoform of heme oxygenase (HO-1), a well-known protein up-regulated during cell stress response, were proposed to be among the strongest positive predictors of metabolic disease, including insulin resistance. Because our group previously reported on levels, activation state and oxidative stress-induced post-translational modifications of HO-1 in AD brain and our ongoing studies to better elucidate the role of HO-1 in insulin resistance-associated AD pathology, the aim of this review is to provide reader with a critical analysis on new aspects of the interplay between HO-1 and insulin resistance and on how the available lines of evidence could be useful for further comprehension of processes in AD brain.

Contents

1. Introduction

Alzheimer disease (AD) is the most common cause of dementia worldwide and due to its multifactorial pathogenesis AD lacks a reliable treatment. According to the Alzheimer Association 2014 report, an estimated 5.2 million Americans of all ages have AD. This includes an estimated 5 million people age 65 and older (Alzheimer's Association, 2014; Hebert et al., 2013) and approximately 200,000 individuals under age 65 who have early-onset AD (Alzheimer's Association, 2006). AD prevalence varies with age: the percentage of people with diagnosed AD is 11% in people age 65 and older (Alzheimer's Association, 2014), whereas AD prevalence is close to 50% in people age 85 and older (Hebert et al., 2013). In addition, of those with AD, the vast majority (82%) are age 75 or older (Alzheimer's Association, 2014; Hebert et al., 2013). Interestingly, almost two-thirds of Americans with AD are women (Alzheimer's Association, 2014; Hebert et al., 2013). Based

Abbreviations: IGF-1, insulin growth factor isoform 1; IR, insulin receptor; IRS-1, insulin receptor substrate isoform 1; HO-1/2, heme oxygenase isoform 1 or 2; BVR-A, biliverdin reductase isoform A; MCI, mild cognitive impairment; PCAD, preclinical Alzheimer disease; HFD, high fat diet; OS, oxidative stress; ROS, reactive oxygen species; RNS, reactive nitrogen species; HNE, 4-hydroxy-2-nonenal; PC, protein carbonyls; 3-NT, 3-nitrotyrosine

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on estimates from ADAMS, among people age 71 and older, 16% of women have AD and other dementias compared with 11% of men (Plassman et al., 2007; Seshadri et al., 1997).

While prevalence is the number of existing cases of a disease in a population at a given time, incidence is the number of new cases of a disease that develop in a given period of time in a defined population. Approximately 469,000 people age 65 or older will develop AD in the United States in 2015 (Alzheimer's Association, 2014). The number of new cases of AD increases dramatically with age: in 2014, approximately 59,000 new cases among people age 65 to 74, 172,000 new cases among people age 75 to 84, and 238,000 new cases among people age 85 and older (the "oldest-old") were predicted. (Alzheimer's Association, 2014; Hebert et al., 2001). Though some studies have reported that incidence rates do not continue to rise after age 90, at least one large study indicates that previous observations of a leveling off of incidence among the oldest-old may be due to sparse data for this group. (Corrada et al., 2010). Because of the increasing number of people age 65 and older in the United States, particularly the oldest-old, the annual number of new cases of AD and other dementias is projected to double by 2050 (Hebert et al., 2001). Indeed, on average, every 67 s, someone in the United States develops AD (Alzheimer's Association, 2014), and by mid-century, someone in the United States will develop AD every 33 s (Alzheimer's Association, 2014).

These numbers are fearful and impact consistently on the care of AD patients, which requires an increasing amount of financial resources. The average annual per-person payment for health care and long-term care services is estimated to be about $50,000. Thus, AD represents not only medical and family problems but also an enormous financial problem. Estimates are that delaying the onset of AD by 5 years would decrease its prevalence by 50%. Given that, it is clear that the impact on the financial resources involved in the care of AD will be enormous. However, despite intensive worldwide research efforts, current treatments have only marginal symptomatic benefits and there are no effective disease-modifying or preventive interventions. Therefore, it is incumbent to better understand the biochemical mechanisms related to the earlier phases of AD before onset of clinical signs and symptoms.

2. Insulin resistance and oxidative stress hypothesis of AD

Insulin resistance is clinically defined as the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in an individual compared to the normal population (Lebovitz, 2001). In 1978, Havrankova et al. showed that insulin is present in rat brain in high concentration, and the brain level is independent of peripheral insulin levels (Havrankova et al., 1978). Thus, although pancreatic-derived insulin crosses the BBB and reaches the brain, a portion of the insulin in the CNS is locally produced, based on the detection of c-peptide (which is an integral part of the pro-insulin molecule) and insulin mRNA in the brain (Ghasemi et al., 2013).

On a molecular level, several targets of the insulin machinery with potential influence on the development of neurodegenerative disease have been identified. Insulin and insulin growth factor-1 (IGF-1) have intense effects in the CNS, regulating key processes such as energy homeostasis, neuronal survival, longevity, learning and memory (Freude et al., 2009; Plum et al., 2005). Insulin and IGF-1 bind to the tyrosine kinase receptors, IR and IGF-1R, which share a high degree of identity in their structure and function (Freude et al., 2009; Plum et al., 2005). IR and IGF-1R are selectively distributed in the brain with a higher density in the olfactory bulb, hypothalamus, as well as in two of the main brain areas affected by AD pathology, i.e., hippocampus and cerebral cortex (Freude et al., 2009; Plum et al., 2005). Binding of insulin or IGF-1 induces a conformational change of the respective receptors leading to their auto-phosphorylation on specific tyrosine residues on the β-subunit with the consequent recruitment of the insulin receptor substrate-1 (IRS-1) (Freude et al., 2009; Plum et al., 2005). This latter, in turn, activates two main signaling pathways: (i) the phosphoinositide-3-kinase (PI3K) pathway, which, among other functions, is involved in the maintenance of synaptic plasticity and memory consolidation (Horwood et al., 2006), Aβ-induced memory loss (Chiang et al., 2010), synthesis of nitric oxide (NO), which in turn plays a role in learning and memory processes (Calabrese et al., 2007); and (ii) the mitogen-activated protein kinase (MAPK) cascade, which is responsible both for the induction of several genes required for neuronal and synapse growth, maintenance and repair processes, and for serving as a modulator of hippocampal synaptic plasticity that underlies learning and memory (Akter et al., 2011) (Fig. 1).

Given the above background, the AD brain is characterized by defective insulin signaling, thus opening a debate about the contribution of brain insulin resistance to AD pathology development (Butterfield et al., 2014a; Cholerton et al., 2013; De Felice, 2013; De Felice et al., 2014; Hoyer, 2002; Perluigi et al., 2014). Indeed, AD patients show reduced brain insulin receptor sensitivity (Rivera et al., 2005; Talbot et al., 2012), hypophosphorylation of the insulin receptor and downstream second messengers such as IRS-1 (Steen et al., 2005; Talbot et al., 2012) and attenuated insulin and IGF-1 receptor expression (Steen et al., 2005). Furthermore, reduced cerebrospinal fluid (CSF) insulin levels have been observed in moderate and severe cases of AD (Craft et al., 1998); however, this research is not conclusive. Other studies have demonstrated either normal (Molina et al., 2002b) or increased CSF insulin levels in AD patients (Fujisawa et al., 1991). Moreover, in the only existing study measuring CSF insulin levels in AD brains that explicitly used age-matched healthy control brains, normal levels of the hormone were detected (Frolich et al., 1998). Similar findings have been reported for insulin and IGF-1R expression — evidence for attenuated levels (Steen et al., 2005), but also evidence for normal or increased levels exists (Frolich et al., 1998; Talbot et al., 2012). Similarly, the evaluation of insulin signaling in the brain of Down syndrome (DS) patients (who are characterized by an increasing risk to develop AD with age because the trisomy of chromosome 21) revealed a marked insulin resistance, which was associated with an increased risk to develop AD (Butterfield et al., 2014b; Perluigi et al., 2014).

Although insulin resistance is now widely accepted to be one of the major risk factors for driving the progression of AD pathology, the mechanisms that underlie this process are not fully elucidated. The idea of oxidative stress (OS) as a link between insulin resistance and AD is currently under evaluation by several research groups including ours (Butterfield et al., 2014a) (Fig. 1). Both insulin resistance and AD have common pathogenic factors, and evidence suggests a close link for the presence of cellular OS, mitochondrial abnormalities and paucity of antioxidant defenses (Butterfield et al., 2014a; Craft, 2005; de la Monte, 2009; Zhao and Townsend, 2009). Since mitochondria are the central coordinators of energy metabolism and are sources and targets of ROS, their impairment may represent a downstream event of insulin resistance and/or AD-associated abnormal brain insulin and glucose metabolism (Moreira, 2012; Reddy et al., 2009). Indeed, increased OS leads to the inhibition of cellular energy production and to the reduction of both insulin secretion and sensitivity (Gerbitz et al., 1996; Moreira et al., 2007). In turn, defective insulin signaling makes neurons energy-deficient and more vulnerable to oxidizing insults, which could promote structural and functional alterations of mitochondria (de la Monte, 2009; Neumann et al., 2008) (Fig. 1). Moreover, insulin resistance-associated impairments in glucose uptake and utilization are associated with increased ER stress, which, deregulate lipid metabolism, causing accumulation of toxic lipids in the brain (de la Monte and Tong, 2014) (Fig. 1).

In that regard, among the mechanism(s) proposed to explain insulin resistance in AD, one of the most conceivable pathways suggests that activation of neuronal TNF-α receptor induces aberrant activation of stress kinases [i.e., Jun N-terminal kinase (JNK), I kappa-B kinase (IKK), and protein kinase R (PKR)] (Bomfim et al., 2012; Lourenco et al., 2013) and ER stress (PKR-mediated phosphorylation of eIF2α-P) (Lourenco et al., 2013). Once activated, these kinases promote serine

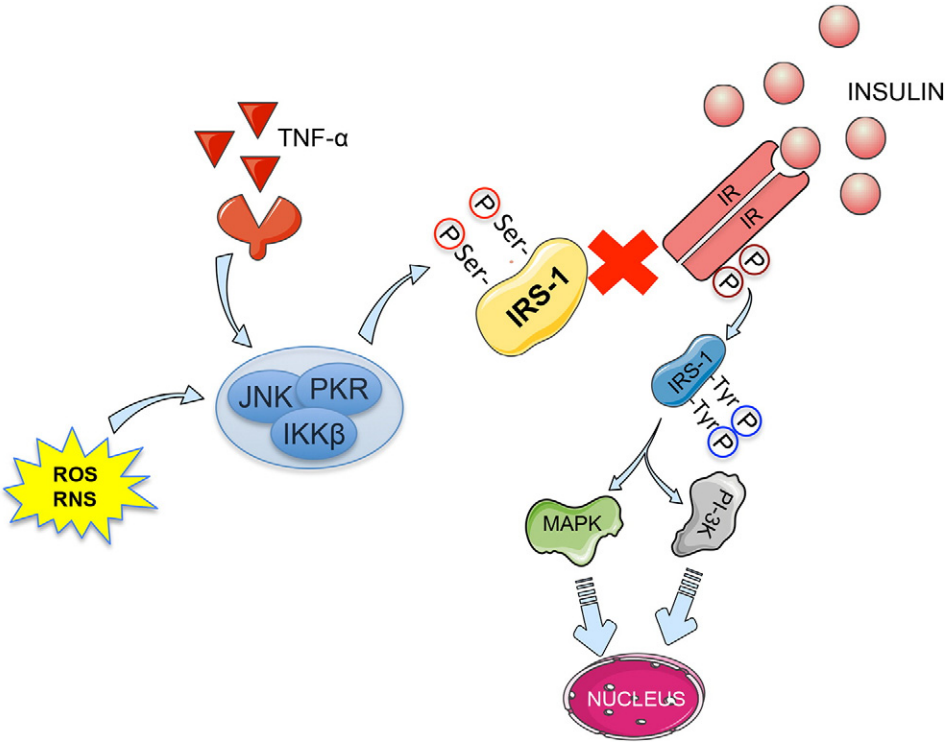

Fig. 1. Mechanism(s) underlying insulin resistance. Under normal conditions binding of insulin to the membrane resident insulin receptor (IR) promotes IR activation through IR dimerization and autophosphorylation of specific tyrosine (pTyr) residues. Stimulation of IR kinase activity is then followed by tyrosine phosphorylation of a variety of endogenous substrates, including the cytosolic insulin receptor substrate (IRS)-1. These events lead to the activation of multiple signaling pathways required for insulin's pleiotropic action, including: (i) the phosphoinositide-3-kinase (PI3K) pathway; and (ii) the mitogen-activated protein kinase (MAPK) pathway, which finally result in the promotion of glucose uptake, glycogen synthesis, mitogenesis, gene expression or cell stress response. However, under pathological conditions including diabetes, metabolic syndrome and Alzheimer disease (AD) a dysfunction of insulin signaling can occur, frequently identified as insulin resistance. On a molecular level, one of the main mechanisms responsible for insulin resistance is the inactivation of IRS-1 through the phosphorylation of specific serine residues (pSer) including Ser307 or Ser612 in rodent (Ser312 and Ser616 in human IRS-1). Dampening insulin signaling results in impaired glucose transport (reduced translocation of the glucose transporter at the plasma membrane) and metabolism, thus promoting an alteration of mitochondrial processes involved in energy production. In turn, impairment of mitochondria functions leads to a vicious circle in which reduced energy production is associated with an increase of ROS and RNS (oxidative stress) and endoplasmic reticulum (ER) stress. In this scenario, increased oxidative/nitrosative stress levels and the activation of neuronal tumor necrosis factor (TNF)-α receptor seem to be responsible for an aberrant activation of stress-induced kinases [i.e., Jun N-terminal kinase (JNK), I kappa-B kinase (IKK), and protein kinase R (PKR)] that promote serine phosphorylation of IRS-1, thereby inhibiting insulin-induced IRS-1 tyrosine phosphorylation.

phosphorylation of IRS-1, thus inhibiting insulin-induced IRS-1 tyrosine phosphorylation. This interferes with the ability of IRS-1 to engage in insulin signaling and blocks the intracellular actions of insulin (Fig. 1). Reduced insulin signaling would increase neuronal vulnerability to synapse damage induced by Aβ (Swomley et al., 2014), ultimately leading to memory impairment (Bomfim et al., 2012; De Felice and Ferreira, 2014; Ma et al., 2009; Talbot et al., 2012).

Therefore, it is likely that a complex signaling network closely connected to oxidative stress and mitochondrial dysfunction leads to impaired insulin signaling in AD.

3. Cell stress response in AD: the dual nature of heme oxygenase

An Alzheimer disease brain has more oxidative damage than a normal brain, exhibits an increased susceptibility to oxidative stress and has relatively low levels of naturally occurring antioxidants such as α-tocopherol (Butterfield et al., 2001; Di Domenico et al., 2014). Aβ peptides, together with altered mitochondrial function, and the presence of trace metal ions such as iron and copper, have been identified as potential sources of oxidative stress (Butterfield et al., 2001; Cai et al., 2011; Clark et al., 2010; Reddy et al., 2009). In accordance with the Aβ-induced oxidative stress hypothesis, oxidative stress is the result of Aβ insertion as oligomers into the bilayer causing ROS production and initiating lipid peroxidation and protein oxidation in AD pathology (Butterfield et al., 2001, 2007, 2013; Butterfield and Lauderback, 2002; Halliwell, 2006) (Fig. 2). Studies on AD transgenic animal models expressing Aβ peptide confirmed the association between Aβ and oxidative stress, suggesting the involvement of methionine 35 of Aβ peptide in the mechanism of oxidative damage (Butterfield et al., 2010, 2013; Sultana et al., 2012).

Because of the role of oxidative stress in AD pathology onset and progression (Butterfield et al., 2001; Di Domenico et al., 2011; Halliwell, 2006; Hensley et al., 1995; Lovell et al., 2001; Mark et al., 1997; Markesbery, 1997; Smith et al., 1994, 1997), most of the studies conducted in the past focused on the comprehension of impaired protective mechanisms leading to Aβ/Tau accumulation in the brain and on how to rescue the antioxidant defenses with the aim to slow the observed neurodegeneration (Barone et al., 2014a; Butterfield et al., 2014a; Di Domenico et al., 2014; Mancuso et al., 2012a, 2012b).

The heme oxygenase/biliverdin reductase (HO/BVR) system is one of the main and evolutionarily conserved cellular cytoprotectants, whose up-regulation represents an early event in the adaptive response to stress (Poon et al., 2004). Humans and rodents have two HO isozymes, namely HO-1 (about 32 kDa, enzyme) and HO-2 (36 kDa). Heme oxygenase-1, also known as heat shock protein (Hsp)-32, is induced by various stimuli, including reactive oxygen species (ROS) and reactive oxygen species (RNS), ischemia, heat shock, bacterial lipopolysaccharide (LPS), hemin, the neuroprotective agent leteprinim potassium (Neotrofin) (Maines, 1997, 2000) and several drugs currently used in the clinic, such as statins, non-steroidal anti-inflammatory drugs, antagonists to the adrenergic β receptor, and cyclosporin A. (Butterfield et al., 2012; Mancuso and Barone, 2009). Heme oxygenase-2, the constitutive isoform, is responsive to developmental factors, adrenal glucocorticoids, nitric oxide (NO) (Maines, 1997), atorvastatin

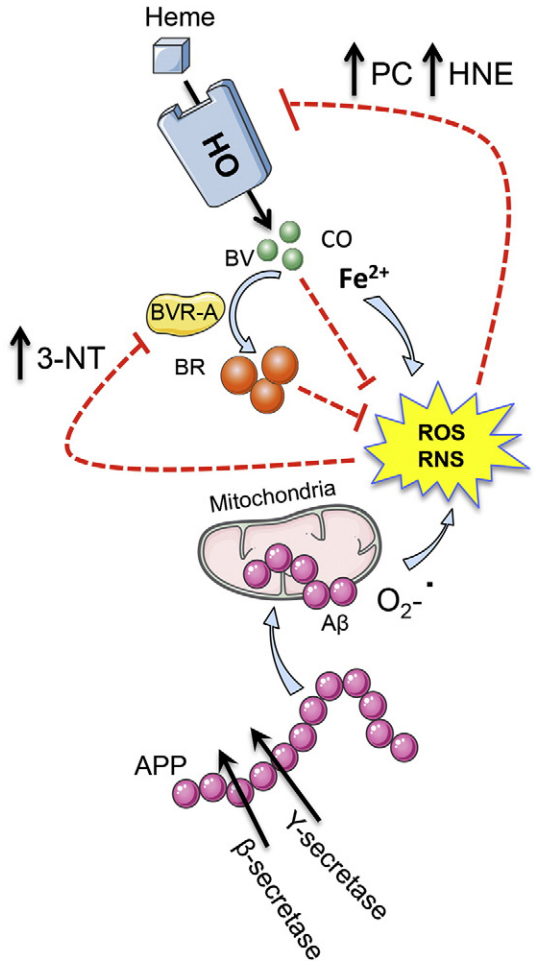

Fig. 2. Hypothesized mechanism(s) underlying the dual nature of the heme oxygenase (HO)/biliverdin reductase-A (BVR-A) system in Alzheimer disease (AD). One of the main hallmarks of Alzheimer disease (AD) is the overproduction and accumulation of amyloid beta (Aβ) peptides (monomers, oligomers, fibrils) in the brain. Aβ peptides are derived from amyloid precursor protein (APP), a type I membrane protein that undergoes a first cleavage by β-secretase and a second one by γ-secretase (an intramembrane aspartyl-protease) to generate Aβ. Increased Aβ production is associated with the elevation of oxidative stress levels mainly due to Aβ-induced mitochondrial impairment and the subsequent over-production of reactive oxygen species (ROS)/reactive nitrogen species (RNS) responsible for increased lipid peroxidation and protein oxidation. These last two are associated with if not responsible for the neuronal dysfunction and death observed in AD. As outlined in the main text the up-regulation of the heme oxygenase (HO)/biliverdin reductase-A (BVR-A) system is one of the earliest events in the adaptive response to stress. Indeed, the membrane resident HO promotes the degradation of extracellular toxic heme into equimolar amount of carbon monoxide (CO), ferrous iron [Fe^{2+}] and biliverdin (BV). This latter is further reduced by the cytosolic BVR-A to bilirubin (BR). Because Fe^{2+} is a well-know pro-oxidant agent whereas both BV and BR at physiological concentrations are potent antinitorsative and antioxidant molecules, the comprehension of the role of the HO/BVR-A system during AD pathology was debated for a long time. These two theories have been reconciled by showing that following the elevation of oxidative stress in AD brain, both HO-1 and BVR-A undergo a series of post-translational modifications [increased protein carbonyls (PC) and 4-hydroxy-2-nonenal (HNE) adducts for the former, and increased 3-nitrotyrosine (3-NT) adducts for the latter], which impair their activity and finally result in the same place as that proposed by the neurotoxic hypothesis associated with the HO/BVR system: damage to AD and MCI brain, including oxidative damage.

(Butterfield et al., 2012) and drugs acting on the nervous system, such as morphine and glucocorticoids (Mancuso and Barone, 2009).

HO-1 and HO-2 catalyze the same reaction, namely the transformation of iron-protoporphyrin-IX-alpha (heme) into equimolar amount of ferrous iron [Fe^{2+}], carbon monoxide (CO), and biliverdin-IX-alpha (BV-alpha) (Maines, 1997, 2000) (Fig. 2). Notwithstanding their common features, HO-1 and HO-2 seem to play different roles in protecting tissues against injuries (Maines, 2005a; Maines and Panahian, 2001). The most convincing hypothesis suggests that controlled HO-1 induction plays a pivotal role in the earliest stages of cellular responses to tissue damage, whereas HO-2 is constitutively expressed and is primarily involved in maintaining cell heme homeostasis and in sensing the intracellular levels of gaseous compounds including oxygen, nitric oxide (NO), and CO (Maines, 2005a). Most heme proteins contain an iron-protoporphyrin moiety as a structural component for their activity and functions. In mammals, hemoglobin is a major supplier of heme protein, while myoglobin, microsomes and catabolic enzymes are the secondary contributors of heme proteins (Tsiftsoglou et al., 2006). High levels of heme are cytotoxic; thus, heme is tightly regulated at level of its biosynthesis by aminolevulinic acid synthase (Tsiftsoglou et al., 2006) and degradation by HO enzymes (Tenhunen et al., 1969a, 1969b).

Similar to HO, two isoforms of BVR were described and named BVR-A and BVR-B (Kapitulnik and Maines, 2009; Maines, 2005b; Pereira et al., 2001). Both these enzymes generate bilirubin, but only BVR-A reduces BV-alpha into the powerful antioxidant and antinitrosative molecule BR-IX-alpha (thereafter BR) (Barone et al., 2009; Stocker, 2004) (Fig. 2). BVR-A not only transforms BV into BR (by reducing the former's C10 [γ bridge]), but BVR-A is also a serine/threonine/tyrosine kinase involved in various cellular functions regulating cell stress response (Kapitulnik and Maines, 2009; Maines, 2005b).

To note, the six players (i.e., HO-1, HO-2, CO, Fe^{2+}, BV, BVR-A and BR) of the HO/BVR-A system could potentially modulate a great number of redox-signaling pathways activated during cell stress-response, thus making this system very interesting for its therapeutic potential (Barone et al., 2014b; Durante, 2010, 2011; Hosick and Stec, 2012; Maines, 2010; Mancuso and Barone, 2009).

With regard to AD, HO-1 overexpression was considered for a long time to be a protective mechanism (Calabrese et al., 2006; Dore et al., 1999; Mueller et al., 2010; Poon et al., 2004; Takahashi et al., 2000) because increased HO-1 levels have been hypothesized to be a direct response to increased free heme associated with neurodegeneration and an attempt to convert the highly damaging heme into the antioxidant BR (Calabrese et al., 2003; Dore, 2002; Dore et al., 1999; Kim et al., 2006; Kimpara et al., 2000; Mancuso et al., 2012a; Takahashi and Snyder, 2000) (Fig. 2).

In addition, increased HO-1 protein levels were also invoked as a conceivable result following the observed decreased levels of constitutive HO-2 protein in AD brain in order to avoid the cytotoxic effects of heme (Barone et al., 2012a; Calabrese et al., 2006). However, little, if any, substantial recovery from oxidative stress-associated pathology is observed in AD brain [reviewed in (Barone et al., 2014b)]. In addition, other groups posited a detrimental activity of HO-1, opining that Fe^{2+} accumulation and attendant oxidative stress and neuronal dysfunction in AD may represent downstream effects of sustained HO-1 overactivity within the astrocyte compartment (Hascalovici et al., 2009; Schipper, 2011; Smith et al., 1997; Takeda et al., 2004) (Fig. 2).

Interestingly, these two apparently contradictory hypotheses were reconciled by the observation of an oxidative-induced impairment of the HO/BVR-A system in AD brain (Barone et al., 2011a, 2011b, 2012a, 2012b, 2014b; Butterfield et al., 2012; Di Domenico et al., 2012) (Fig. 2). Indeed, this view results in the same place as that proposed by the neurotoxic hypothesis associated with the HO/BVR system: damage to AD and MCI brain, including oxidative damage. Hence, we suggest that it is time to come together and agree that both notions lead to the same conclusion: oxidative damage in AD and MCI brain, produced in part either as a result of the products of HO-1 (ferrous iron for example) or as a result of a dysfunctional HO/BVR system as a consequence of oxidative and/or nitrosative modification. The challenge in AD and its earlier forms [MCI and preclinical Alzheimer disease (PCAD)] will be to find an effective pharmacological treatment that is conceivably capable of overcoming or at least reducing these obstacles related to neurotoxic effects.

4. Does heme oxygenase drive insulin resistance in AD?

Despite being known for some time [HO was first discovered in 1968, (Tenhunen et al., 1968)], the HO protein is still being studied to investigate potential unknown properties in addition to the simple degradation of heme (Barone et al., 2014b; Dennery, 2014; Motterlini and Foresti, 2014; Wegiel et al., 2014). In particular, both HO isoenzymes and their by-products were reported to play a role in insulin signaling, shedding light on the impairment of this important antioxidant response as a central event in the development of insulin resistance (Mishra and Ndisang, 2014; Ndisang, 2010).

Because insulin resistance represents the source of pathogenesis driving metabolic syndrome, this latter defined as a cluster of conditions – increased blood pressure, a high blood sugar level, excess body fat around the waist and abnormal cholesterol levels – that occur together, increasing the risk of heart disease, stroke, obesity, diabetes and AD (Butterfield et al., 2014a; Craft, 2005; Craft et al., 1998; De Felice, 2013; de la Monte, 2009; Frolich et al., 1998; Hoyer, 2002; Molina et al., 2002a; Moreira, 2012; Shin et al., 2013), a wide literature described the involvement of HO in insulin resistance especially in peripheral organs deputed to insulin production and glucose metabolism [reviewed in (Mishra and Ndisang, 2014; Ndisang, 2010)]. Conversely, because the hypothesis that insulin resistance develops in the brain and could drive AD-associated pathology is something quite new, only a few studies addressed the involvement of the HO/BVR-A system as part of this impaired pathway.

The first study demonstrating a link between insulin signaling and HO in the CNS appeared in 2000 with the aim to characterize the role of HO in cell injury, and to investigate whether topical application of IGF-1 could influence HO-2 expression in spinal cord injury (Sharma et al., 2000). Interestingly, 10 ng/μL of IGF-1 topically applied 30 min before and 30–240 min after spinal cord injury in rats reduced injury-induced HO-2 overexpression in nerve cells and dendrites (Sharma et al., 2000). This study provided evidence for the first time that neurotrophins like IGF-1 inhibit HO-2 overexpression in spinal cord trauma and suggested a conceivable mechanism involving reduction of the injurious HO-2-dependent CO production in the spinal cord (Sharma et al., 2000).

A subsequent study highlighting a connection between insulin signaling and HO protein in neurons was reported only ten years later. Indeed, Hsu and colleagues demonstrated that berberine (BBR) – a well-known anti-diabetic herbal medicine in Asia with beneficial effects on insulin sensitivity, glucose metabolism and glycolysis – had an effect on HO protein expression (Hsu et al., 2012). These researchers identified the critical role of phosphatidylinositol 3-kinase (PI3K)/Akt involved in BBR cellular defense mechanisms and first revealed the novel effect of BBR on nuclear factor (erythroid-derived 2)-related factor-2 (Nrf2)/HO-1 induction in NSC34 neuron-like cells. BBR (0.1–10 nM) led to increasing insulin receptor expression, Akt phosphorylation and enhanced oxidant-sensitive Nrf2/HO-1 induction, which were blocked by a PI3K inhibitor, LY294002 (Hsu et al., 2012). In H_2O_2-treated cells, BBR significantly attenuated ROS production and increased cell viability, antioxidant defense (GSH and SOD) and oxidant-sensitive proteins (HO-1 and Nrf2), which also were blocked by LY294002, thus highlighting that the insulin/PI3K/Akt cascade plays a critical role in BBR-activated Nrf2/HO-1 signaling (Hsu et al., 2012).

In 2013, Lu et al. reported on the role of resistin – an adipose tissue-specific hormone thought to represent a link between obesity and insulin-resistant diabetes – in dopaminergic neurons (Lu et al., 2013). Indeed, both in rodent and human cells, resistin led to decreased response to insulin (Barnes and Miner, 2009). In the former, this is likely in part due to an up-regulation of suppressor of cytokine signaling (SOCS)-3, which interferes with the activation of IRS-1 (Barnes and Miner, 2009). Conversely, in human cells, resistin is expressed primarily by macrophages and seems to be involved in the secretion of pro-inflammatory factors, including tumor necrosis factor (TNF)-α, which as highlighted in the previous section seems to be one of the main mediators of insulin resistance (Barnes and Miner, 2009). Interestingly, these authors showed that resistin (2–10 ng/mL) protected against 6-hydroxydopamine (6-OHDA, 75 μM)-induced cell death in dopaminergic-like MES23.5 cells (Barnes and Miner, 2009). These scientists also showed that resistin induced up-regulation of HO-1 and Hsc (heat shock cognate) 70 (Barnes and Miner, 2009). The protective effect of resistin on 6-OHDA-induced cell death was abolished by the HO-1 inhibitor zinc protoporphyrin IX and HSP inhibitor KNK437 (Barnes and Miner, 2009). These results suggest the neuroprotective effects of resistin against 6-OHDA-induced cell death are associated with the underlying mechanisms of inhibiting oxidative stress and apoptosis. Unfortunately, despite the link between resistin and insulin resistance, this latter study did not evaluate any aspect of insulin signaling with regard to this resistin-associated neuroprotective effects, thus leaving an open question about whether the induction of the HO-1 occurs via the insulin/PI3K/Akt pathway as for berberine (Hsu et al., 2012) or not. Therefore, notwithstanding that the above-cited studies hypothesized a link between HO protein and insulin signaling in neurons, which indeed would represent a new and intriguing signaling pathway, the exact mechanism(s) linking HO levels and activity to the insulin cascade remain to be elucidated.

Because (i) both spinal cord injury and resistin were associated with increased insulin resistance (Barnes and Miner, 2009; Qin et al., 2010), and (ii) IGF-1 reduces HO-2 protein levels (Sharma et al., 2000), it is conceivable that the levels of HO proteins would parallel with insulin resistance in neurons. In that regard, a very recent study by Jais et al. (2014) suggested that in matched biopsies from "healthy" versus insulin-resistant obese subjects HO-1 is among the strongest positive predictors of metabolic disease in humans (Jais et al., 2014). Furthermore, these authors found that hepatocyte and macrophage conditional HO-1 deletion in mice evokes resistance to diet-induced insulin resistance and inflammation, dramatically reducing secondary disease such as steatosis and liver toxicity (Jais et al., 2014). These results suggest that HO-1 is necessary for the development of metaflammation and metabolic disease, and call for a re-evaluation of numerous findings in the field (Jais et al., 2014). However, an alternative explanation could be that HO-1 elevation is a compensatory response to metaflammation and oxidative stress.

Even though this latter study did not employ brain biopsies, because the ability of HO-1 to be induced by a variety of stressors in an equally wide variety of tissues and cell types (Dunn et al., 2014), it would not be surprising to see in the near future that brain insulin resistance could be associated with increased HO-1 levels. Such studies are ongoing in our laboratories.

Interestingly, if we focus on another disease characterized by insulin resistance, i.e., diabetes, the few lines of evidence in mice show that HO-1 protein levels are increased in the brain of db/db mice and that this increase parallels the augmentation of isoprostanes and 8-OHdG, markers of lipid peroxidation and DNA oxidation, respectively (Marrazzo et al., 2011). Similarly, it was observed that ferric nitrilotriacetate (Fe-NTA)-induced diabetes in rats was associated with an increase of HO-1 protein levels in the brain (Nakatsuka et al., 2009).

Based on these data and our experience on the HO-1/BVR-A system in the brain of subjects with AD or MCI (Barone et al., 2011a, 2011b, 2012a, 2012b, 2014b), it becomes difficult to argue a unique hypothesis about the role of HO-1 in insulin resistance in the brain because what is still missing with regard to diabetes or cell-based experiments is evidence about HO activity and/or post-translational modifications.

5. Future directions

The study from Jais et al. (2014) indicates that HO-1 is necessary for the development of metaflammation and insulin resistance and calls into question numerous finding on the field (Jais et al., 2014). Indeed,

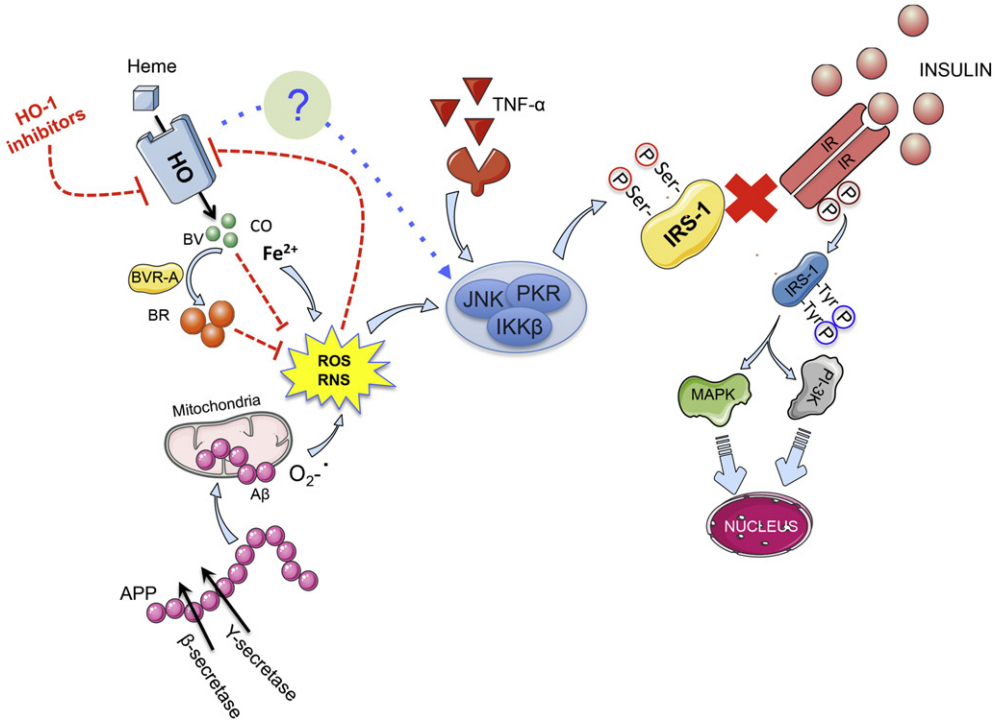

Fig. 3. The interplay between heme oxygenase (HO) and insulin resistance in Alzheimer disease (AD). According to (Jais et al., 2014) HO-1 appears to be one of the strongest positive predictors of metabolic disease. Indeed conditional HO-1 deletion in mice is associated with reduced peripheral insulin resistance and inflammation probably due at least in part to the observed reduction of pro-inflammatory tumor necrosis factor (TNF)-α levels. However, the exact mechanism(s) regulating HO-1-dependent reduction of TNF-α have not been elucidated (?). In addition, because with the progression of AD pathology, the uncontrolled rise of HO-1 could initially sustain the elevation of oxidative stress, which then would promote HO-1 impairment thus finally resulting in a substantial neurotoxic effect (because the maintenance of elevated oxidative stress levels); the effective role of HO has to be better clarified. Many other players different from HO-1, could be responsible for the observed insulin resistance, including oxidative stress. However, the evidence that conditional deletion of HO-1 leads to reduced insulin resistance and to a better functioning of insulin signaling, could be helpful in a scenario accounting for elevated HO-1 levels during the early phase of AD pathology. Indeed, in this case, the use of HO-1 inhibitors could represent a therapeutic strategy to be used during the early phases of AD pathology aimed to rescue HO-1 physiological activity and thus avoid a further increase of oxidative stress. Conversely, in the late phases of the pathology, during which an oxidative stress-induced impairment of HO-1 has been observed, this latter event would paradoxically favor the beneficial action of other kinds of treatments such as intranasal insulin.

one of the aspects which appears to be interesting is that the loss of HO-1 led to significant augmentation and acceleration of key upstream insulin signaling activation events including phosphorylation of both insulin receptor and Akt. Conversely, overexpression of HO-1 triggered glucose intolerance and insulin resistance (Jais et al., 2014). Furthermore, following HO-1 deletion, these mice exhibited a distinct reduction of pro-inflammatory cytokines such as TNF-α with respect to their counterparts fed with a high fat diet (HFD), thus highlighting a possible role of HO-1 in TNF-α-induced insulin resistance (Jais et al., 2014) (Fig. 3).

In our opinion, these lines of evidence obtained in peripheral tissues, open a potentially new means for the comprehension of the mechanism(s) contributing to insulin resistance also in the brain and especially in AD. These results offer a potentially new background on which to reconsider the available data obtained in the brain of both human and mice. Interestingly – even though there is a lack of any critical analyses currently – what appears to be quite clear from the literature is that the brain of AD subjects shows both insulin resistance (Butterfield et al., 2014a; Cholerton et al., 2013; De Felice, 2013; De Felice et al., 2014; Hoyer, 2002; Perluigi et al., 2014) and increased HO-1 protein levels (Barone et al., 2014b; de la Monte, 2009).

However, because the HO-1 protein is also a target of oxidative post-translational modifications, which in turn impair its activity in AD brain (Barone et al., 2012a), it remains to be seen whether HO-1 impairment is an early or a late event in the progression of AD. Based on our data on brain from MCI subjects, it would be likely that HO-1 oxidative modifications appear: (i) to happen even before the clinical signs of AD dementia, and (ii) to parallel an increase of oxidative stress levels (Barone et al., 2012a, 2014b). Whether, this early upregulation of HO-1 is responsible by itself for insulin resistance in AD needs further analyses.

As explained above and reviewed in (Barone et al., 2014b), the expected neuroprotective activity of the HO-1/BVR-A system requires both HO-1 and BVR-A to be active and complementary, thus implying that any imbalance of their activity would result in increased oxidative stress levels in brain. Indeed, also in the study by Jais et al. (2014) increased ROS production was observed following HO-1 deletion (Jais et al., 2014) even though ROS elevation was considered to have positive effects by promoting IR activation (increased insulin signaling) through a ROS-dependent inactivation of the main IR tyrosine phosphatase (PTPN1/PTP1B) (Jais et al., 2014). These effects were reverted by HO-1 overexpression (Jais et al., 2014). In this scenario, the threshold of ROS elevation could represent the discriminant factor by considering that a controlled elevation of ROS has a physiological role (Sena and Chandel, 2012; Valko et al., 2007) while uncontrolled elevated ROS production is detrimental to brain (Butterfield et al., 2001, 2007, 2013, 2014a, 2014b). Likely, the knockout of HO-1 protein: (i) could not be enough to promote a robust increase of oxidative stress levels in the time frame taken into consideration in Jais et al. (2014) and thus to be responsible of brain proteins' impairment as observed in MCI or AD; or (ii) could promote the modulation of other signaling pathways [e.g. SOD2, GPX, NQO1, (Jais et al., 2014)], which would balance at least in part the elevation of oxidative stress. To unravel whether HO-1 knockout is beneficial or not in terms of oxidative stress and insulin resistance needs further analyses including age-dependence studies as well as the evaluation of its close partner BVR-A. Indeed, prolonged HO-1 knockout could be responsible for sustained increase of oxidative stress levels due to the lack of BR antioxidant and antinitrosative features (Barone et al., 2009; Stocker, 2004).

Because either the uncontrolled over-activation (Hascalovici et al., 2009; Schipper, 2011; Smith et al., 1997; Takeda et al., 2004) or the

absence of HO-1 (Agarwal and Nick, 2000; Bishop et al., 2004; Lin et al., 2007; Yet et al., 2003; Zhang et al., 2004) would be detrimental for neurons, to discriminate between two hypothetical phases of AD pathology, one during which the activity of HO-1 is augmented (initial phase?) and the other during which there is significant impairment of HO-1 (simulating HO-1 knockout; late phase), also would be helpful to plan timing and duration of potential therapeutic interventions (Fig. 3).

In conclusion, by considering that intranasal administration of insulin in AD patients was selected by the National Institutes of Health (NIH) as one of two therapeutic strategies receiving substantial funding as part of the National Alzheimer's Plan in the USA aimed to prevent or treat AD by 2025 (Wadman, 2012), data from Jais and colleagues showing increased response to insulin following HO-1 deletion appear even more interesting. In fact, in accordance with a neurotoxic role for HO-1 overexpression in AD (Hascalovici et al., 2009; Schipper, 2011; Smith et al., 1997; Takeda et al., 2004), which could also drive insulin resistance, inhibitors of HO-1 activity conceivably might represent an effective neurotherapeutic intervention (Gupta et al., 2014; Schipper et al., 2009) (Fig. 3). On the other hand, once HO-1 activity is impaired due to oxidative modifications, this would paradoxically favor the effect of insulin. Such studies are underway in our laboratories.

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