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Understanding the link between insulin resistance and Alzheimer's disease: Insights from animal models

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ABSTRACT

Alzheimer's disease (AD) is a devastating neurodegenerative disease affecting millions of people worldwide. AD is characterized by a profound impairment of higher cognitive functions and still lacks any effective disease-modifying treatment. Defective insulin signaling has been implicated in AD pathophysiology, but the mechanisms underlying this process are not fully understood. Here, we review the molecular mechanisms underlying defective brain insulin signaling in rodent models of AD, and in a non-human primate (NHP) model of the disease that recapitulates features observed in AD brains. We further highlight similarities between the NHP and human brains and discuss why NHP models of AD are important to understand disease mechanisms and to improve the translation of effective therapies to humans. We discuss how studies using different animal models have contributed to elucidate the link between insulin resistance and AD.

1. Introduction

Insulin was discovered in 1921 as an hypoglycemic agent isolated from islet beta cells of dogs (Banting and Best, 1922) and for decades it was mainly associated with the regulation of peripheral glucose homeostasis and glucose transporter type 4 (GLUT4) translocation to the plasma membrane (Huang and Czech, 2007; James et al., 1988). Later, studies revealed that insulin could regulate satiety through its action in the hypothalamus (Debons et al., 1969, 1970) and that there was an abundance of insulin receptors in various brain regions (Hopkins and Williams, 1997; Werther et al., 1987; Zhao et al., 1999), suggesting that insulin could target the central nervous system. These findings paved the way for a growing literature on the importance of insulin for a variety of physiological and vital brain functions such as the regulation of feeding behavior, energy maintenance and memory formation (Banks, 2004; Banks et al., 2012; Brüning et al., 2000; Ghasemi et al., 2013).

Conversely, defective insulin signaling has been proposed to play a role in brain dysfunction in neurodegenerative diseases, particularly in Alzheimer`s disease (AD) (De Felice and Ferreira, 2014a, 2014b; Ferreira et al., 2018; Salas and De Strooper, 2018). AD is the most common form of dementia among the elderly population and dramatically impacts the quality of life of both patients and caregivers (Alzheimer's Association, 2017). The two classical pathological hallmarks of AD are extracellular senile plaques, composed mainly of amyloid-β (Aβ) deposits, and intraneuronal neurofibrillary tangles, which are formed when tau protein becomes abnormally phosphorylated (Walker and Jucker, 2017). Markers of insulin resistance have been found in AD brains (Bomfim et al., 2012; Craft, 2012; Moloney et al., 2010; Steen et al., 2005; Talbot et al., 2012), and, since proper

Abbreviations: AD, Alzheimer`s disease; APP, Amyloid precursor protein; Aβ, Amyloid-β; AβOs, Amyloid beta Oligomers; JNK, c-Jun N-terminal kinase; CREB, cAMP response element-binding protein; CSF, Cerebrospinal fluid; ER, Endoplasmic reticulum; eiF2α, Eukaryotic Initiation Factor 2α; GLP-1R, glucagon-like peptide-1 receptor; GSK3β, Glycogen synthase kinase 3β; IRS-1, Insulin Receptor Substrate 1; IR, Insulin receptor; IL1β, Interleukin 1β; IL6, Interleukin 6; IKKβ, IκB kinase; mTORC1, Mammalian target of rapamycin complex 1; MMSE, Mini-Mental State Examination; NHP, Non-human primate; NA, Noradrenaline; IκBα, Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; PIP_3, Phosphatidylinositol (345)-triphosphate; PI3K, Phosphoinositide 3-kinase; peiF2α, Phosphorylated eIF2α; pPKR, Phosphorylated PKR; PSD-95, Postsynaptic density-95 protein; PS1, Presenilin 1; AKT, Protein kinase B; PKR, Protein kinase RNA-activated; SNS, Sympathetic nervous system; TUDCA, Tauroursodeoxycholic acid; ThioS, Thioflavin-S; TNFR1, TNFα type 1 receptor; TNFα, Tumor Necrosis Factor α; T2D, Type 2 diabetes; UPR, Unfolded protein response; WT, Wild-type

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insulin signaling is important for synaptic plasticity and memory-related processes, including the modulation of dendritic spine density (Lee et al., 2011), synaptic formation and transmission, and long-term potentiation (Izumi et al., 2003; Lee et al., 2011; Stranahan et al., 2008), impaired insulin signaling has been proposed to be an important player in AD pathogenesis (Craft, 2012; de la Monte et al., 2009; Zhao et al., 1999). Additionally, hyperinsulinemia has been associated with a higher risk of cognitive decline and AD (Luchsinger et al., 2004; Ma et al., 2016; Schrijvers et al., 2010), and it correlates positively with disease severity in patients with normal blood glucose levels (van Oijen et al., 2008). High fasting blood glucose and reduced cerebrospinal fluid (CSF)/serum insulin ratio are measures associated with peripheral and whole-body insulin insensitivity in humans (Heni et al., 2014) that are observed in AD patients (Craft et al., 1998; Gil-Bea et al., 2010; Janson et al., 2004). This clinical evidence suggests a link between peripheral and/or brain insulin resistance and AD.

In this Review, we discuss valuable insights into the role of insulin resistance in AD, including mediating effects of inflammation and endoplasmic reticular stress. First, we summarize the physiological role of insulin in the brain and review data obtained from studies using mouse models. We then discuss some limitations of currently available experimental animal models of AD and discuss AD-related pathology and insulin signaling impairments observed in a non-human primate (NHP) model of AD developed and characterized by our group (Forny-Germano et al., 2014).

2. Brain insulin signaling

Insulin can be produced primarily in the brain or it can reach this organ by crossing the blood-brain barrier (BBB) after being produced in peripheral tissues (Banks, 2004). Evidence supporting the cerebral production of insulin emerged from reports detecting central expression of preproinsulin (Devaskar et al., 1993, 1994; Gerozissis and Kyriaki, 2003; Schechter et al., 1996; Young, 1986) and the presence of C-peptide, a constituent of the proinsulin molecule that is released upon insulin production (Dorn et al., 1983; Frölich et al., 1998; Jezová et al., 1985). Although depolarizing conditions stimulate insulin release from neurons and synaptosomes (Clarke et al., 1986; Wei et al., 1990), it is not clear to which extent the locally produced insulin affects brain function. Nonetheless, the intravenous delivery of insulin increases the levels of this hormone in the CSF (Wallum et al., 1987), promotes neuronal activity (Rotte et al., 2005) and improves cognition (Kern et al., 2001), indicating a central role for insulin originated from the periphery.

Upon the binding of insulin, its transmembrane tyrosine-kinase receptor activates and recruits Insulin Receptor Substrates (IRS), including the Insulin Receptor Substrate 1 (IRS-1), which is then phosphorylated at tyrosine residues followed by the activation of phosphoinositide 3-kinase (PI3K). IRS-1 phosphorylation at serine residues inhibits the intracellular cascade of insulin signaling and its level can be used as a marker of impaired insulin signaling (Hotamisligil et al., 1996). PI3K activation leads to the formation of phosphatidylinositol (3, 4, 5)-triphosphate (PIP_3) and activation of protein kinase B (AKT) (Fig. 1). Once activated, AKT inhibits glycogen synthase kinase 3β (GSK3β) and activates the mammalian target of rapamycin complex 1 (mTORC1) pathway and the transcription factor forkhead box O (FoxO). In parallel, insulin promotes the extracellular signal-regulated kinase (ERK)/cAMP response element-binding protein (CREB) (Guo, 2014; Hemmings and Restuccia, 2015; Rask-Madsen and Kahn, 2012).

Among the physiological effects of insulin on brain function, this hormone has been shown to be a memory enhancer and a regulator of food intake and body weight in different species (Benedict et al., 2004; Ikeda et al., 1986; Marks et al., 2009; Park et al., 2000; Woods et al., 1979). In humans, intranasal insulin alters peripheral insulin sensitivity and exert anorexigenic effects by increasing the availability of the energy metabolites adenosine triphosphate and phosphocreatine in the brain (Heni et al., 2012; Jauch-Chara et al., 2012). It also modulates auditory evoked potentials, and enhances attention, mood and declarative memory in healthy subjects (Benedict et al., 2004).

The neuronal suppression of the insulin receptor (IR) diminishes synapse number, alters synaptic transmission, affects experience-dependent synaptic plasticity, increases food intake and promotes obesity (Brüning et al., 2000; Chiu et al., 2008). Synaptic plasticity, a pivotal process for memory formation, can be modulated by insulin via N-methyl-D-aspartate (NMDA) receptors (Van Der Heide et al., 2005). Cortical and hippocampal activation of the PI3K-AKT pathway is involved with long-term potentiation and contextual fear conditioning memory (Opazo et al., 2003; Woods et al., 1979). The mTORC1 pathway is involved in long-term memory formation, possibly due to its role in overall protein translation, which is a crucial mechanism implicated with long-term memory storage (Pereyra et al., 2018; Yin et al., 1994). CREB is a transcription factor that modulates spine dynamics, brain connectivity (Pignataro et al., 2015) and is responsible for the upregulation of proteins involved with memory, such as the brain-derived neurotrophic factor (BDNF) (Tao et al., 1998). In the hypothalamus, insulin regulates food intake and peripheral energy homeostasis via PI3K-AKT pathway (Shen et al., 2011; Xu et al., 2010; Yang et al., 2017).

Considering the established physiological role of insulin signaling in the brain, it is reasonable to conclude that a pathological condition marked by insulin resistance will be accompanied by cognitive and metabolic alterations that need to be taken into account when elucidating the disease pathogenesis. Therefore, in the next sections of this review, we discuss evidence of impaired insulin signaling in the brains of AD animal models.

3. Insulin resistance in mouse models of Alzheimer`s disease

Impaired insulin signaling is present in several transgenic and non-transgenic mouse models of AD. In the 3xTgAD model, reduced levels of IRS-1 associated to the membrane of hippocampal extracts (Ma et al., 2009) and decreased activation of IRS-1 and PI3K in the hippocampus and cortex were observed by 10 months of age (Velazquez et al., 2017). Interestingly, the 3xTgAD model exhibits memory deficits as early as 2 and 6 months of age, while peripheral glucose and insulin dysregulation only appears at 10 months of age (Stevens and Brown, 2015; Stover et al., 2015; Vandal et al., 2015). The APP/PS1 model has higher levels of IRS-1 phosphorylated in serine 616 in the hippocampus at 9 months of age (Long-Smith et al., 2013), and increased levels of IRS-1 phosphorylated in serine 636 and 312 in the frontal cortex at 13 months (Bomfim et al., 2012). Markers of insulin resistance were also reported in the hypothalamus of APP/PS1 mice (Ruiz et al., 2016). After a fasting-refeeding protocol, 5 to 6 month-old APP/PS1 mice show decreased activation of hypothalamic AKT and GSK3β, when compared to control wild-type (WT) animals exposed to the same protocol (Ruiz et al., 2016). Contextual memory was impaired in the APP/PS1 mice as early as 6 months of age and peripheral metabolic impairment started at 10 weeks of age (Kilgore et al., 2010; Zhang et al., 2012). Increased inhibitory phosphorylation of IRS-1 in serine 612 was also observed in the hippocampus of 5-month-old tg2576 mice, in combination with peripheral insulin resistance (Velazquez et al., 2017). In addition, the 5xFAD transgenic AD model has increased levels of inhibitory serine phosphorylation of IRS-1 in the hippocampus at 3 months of age (Kaminari et al., 2017).

A non-transgenic mouse model of AD (AβO-injected mice) can be induced by the intracerebroventricular (icv) injection of amyloid-β oligomers (AβOs), pivotal toxins that build up in the brains of AD patients. AβO-injected mice, similar to transgenic animals (APP/PS1, 3xTgAD), show markers of insulin resistance in the brain and in peripheral tissues (Bomfim et al., 2012; Clarke et al., 2015). Increased phosphorylation of IRS-1 at serine 636 is present in the hippocampus 7 days after one single injection of AβOs (Lourenco et al., 2013). Markers

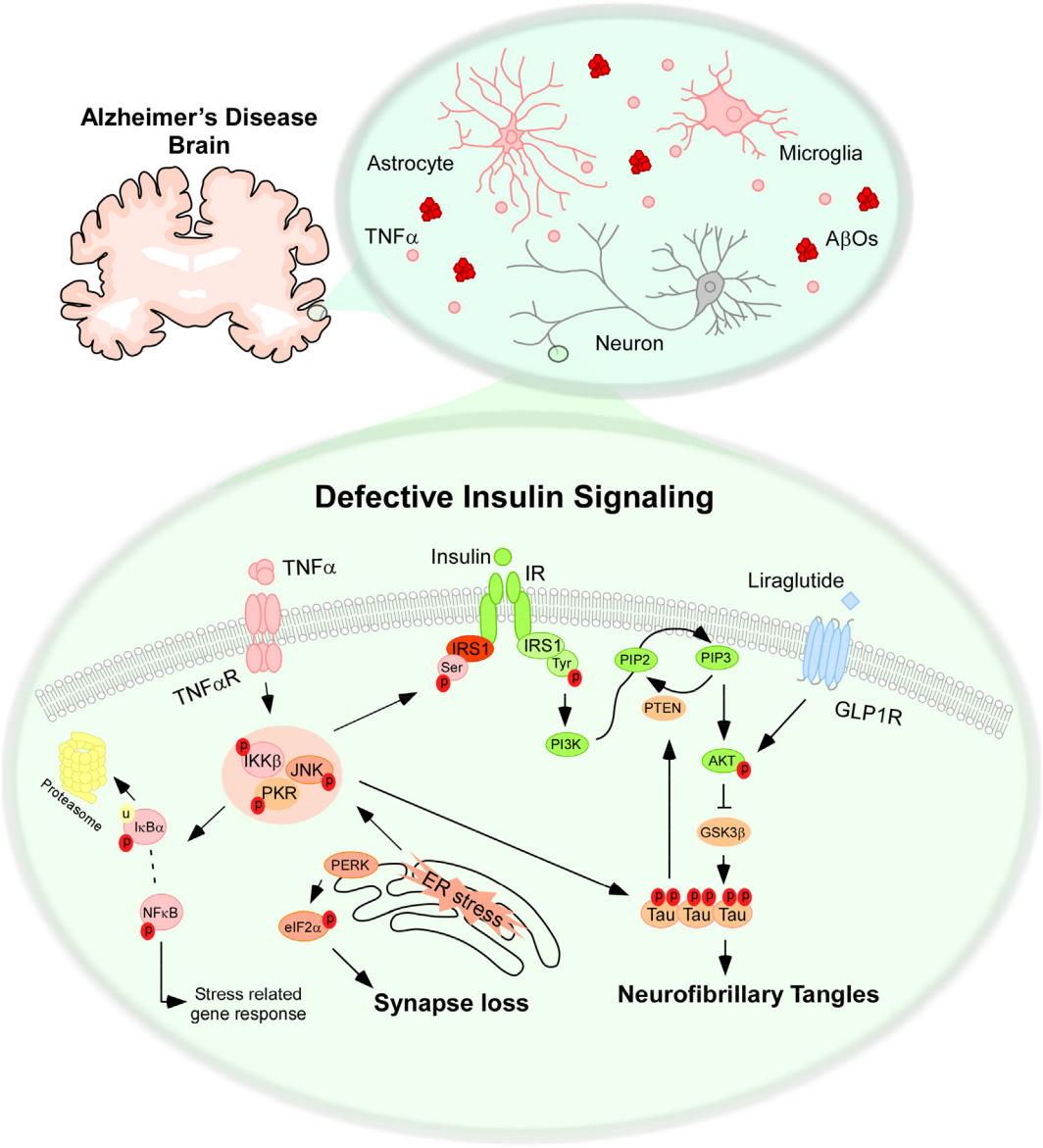

Fig. 1. Molecular mechanisms underlying defective insulin signaling in Alzheimer's disease (AD). Evidences indicate that the overproduction of Aβ activates an immune response that involves microglia and astrocyte recruitment in different brain areas. Over-activation of these cells will produce elevated levels of TNFα, which induces the activation of IKKβ, degradation of NFκB inhibitor α (IκBα) by the proteasome and translocation of the NFκB to the nucleus. In the nucleus, NFκB will act as a transcriptional factor of genes, mediating pro-inflammatory responses. Inflammation and endoplasmic reticulum (ER) stress will trigger PKR and JNK phosphorylation and activation. pIKKβ, pPKR and pJNK will promote the phosphorylation of insulin receptor substrate 1 (IRS-1) in serine residues, impairing insulin signaling. Elevated levels of phosphorylated eukaryotic translation initiation factor α (eIF2α) will decrease translation and promote synapse loss. pPKR, pJNK and decreased insulin signaling will promote tau phosphorylation and neurofibrillary tangle formation. Tau aggregation into neurofibrillary tangles can impact insulin signaling by loss of the physiological role of tau inhibiting PTEN. Liraglutide, an GLP1-R agonist is able to restore insulin signaling and is a potential therapy for AD. TNFα: tumor necrosis factor α; IKKβ: IκB kinase; NFκB : nuclear factor κB; Protein kinase RNA-activated: PKR; Janus kinase: JNK; insulin receptor substrate 1: IRS-1; phosphoinositide 3-kinase: PI3K; phosphatidylinositol (3, 4, 5)-triphosphate: PIP3; phosphatidylinositol-4 5-bisphosphate: PIP2; protein kinase B: AKT; glycogen synthase kinase 3β: GSK3β; eukaryotic translation initiation factor α: eIF2α; Phosphatase and tensin homolog: PTEN; glucagon-like peptide-1 receptor: GLP1R; phosphorylation: p.

of insulin resistance were also observed in the hypothalamus of AβO-injected mice (Clarke et al., 2015; Ruiz et al., 2016) in combination with an ablation of the typical effect of insulin in decreasing food intake. Interestingly, the central infusion of AβOs lead to peripheral insulin resistance, which was further observed in the APP/PS1 and in the 3xTgAD mouse models of AD (Clarke et al., 2015).

Hypothalamic insulin signaling activates ATP-sensitive potassium channels (K_{ATP} channels) and ultimately promotes neuronal hyperpolarization (Spanswick et al., 2000). This event decreases the sympathetic nervous system (SNS) outflow to peripheral tissues, such as liver and white adipose tissues (WAT), and modulates gluconeogenesis and lipolysis (Pocai et al., 2005; Scherer et al., 2012). Therefore, impaired hypothalamic insulin signaling increases the SNS outflow to peripheral tissues and augments plasma noradrenaline (NA) levels, which could increase blood glucose and favor metabolic changes (Bruce et al., 1992). Interestingly, high NA levels are observed in the plasma of AD patients (Lawlor et al., 1995; Oka, 2009; Raskind et al., 1984) and mouse models (Clarke et al., 2015). Therefore, hypothalamic insulin resistance could be a molecular mechanism that contributes to peripheral metabolic changes observed in AD (Fig. 2).

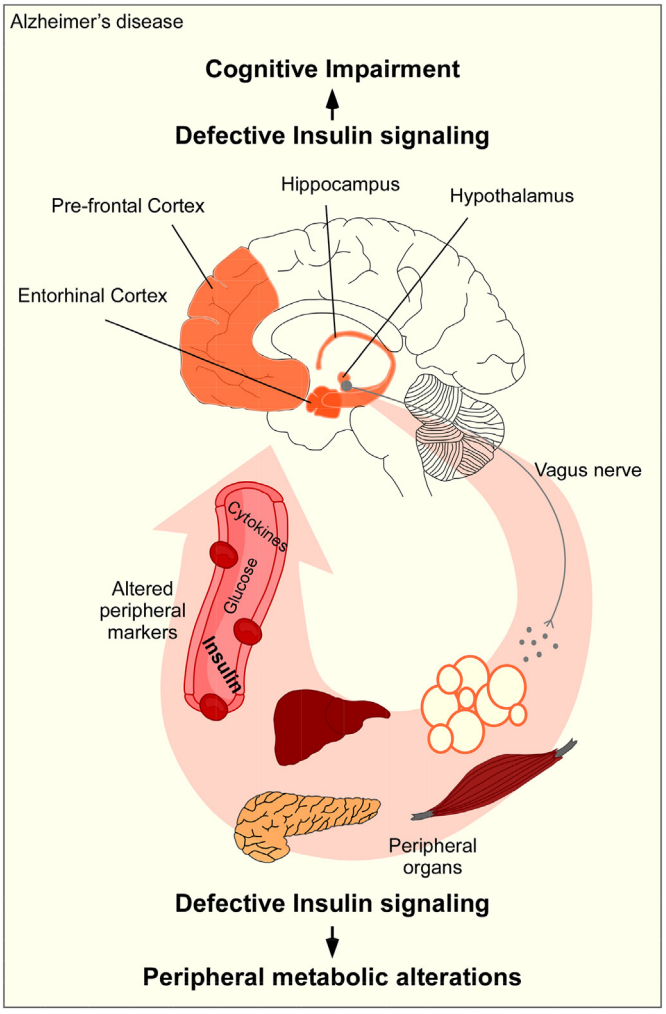

Fig. 2. Model of cross-talk between the brain and the periphery promoting Alzheimer's disease (AD). Impaired insulin signaling in the brain of AD patients promote cognitive decline. Hypothalamic insulin resistance would trigger peripheral metabolic alterations that would aggravate AD condition.

3.1. Inflammation

Insulin can modulate the secretion of cytokines by astrocytes and microglia and, therefore, affect inflammatory processes (Guo, 2014; Spielman et al., 2015). Alternatively, inflammation can act as a negative regulator of the insulin pathway by triggering insulin signaling defects in the brain and in peripheral tissues (Dandona et al., 2004; De Felice and Ferreira, 2014; Odegaard and Chawla, 2013). Chronic systemic inflammation has been linked to cognitive decline and may play a role in AD pathophysiology (Bradshaw et al., 2013; De Felice et al., 2014; De Felice and Ferreira, 2014; De Felice and Lourenco, 2015; Ferreira et al., 2018; Heneka et al., 2015a, 2015b; Laske et al., 2010; Lue et al., 2001; Medeiros and LaFerla, 2013; Olabarria et al., 2010; Zimmer et al., 2014). In line with that, studies using mouse models have helped to elucidate the link between this important feature of AD and insulin resistance.

Tumor Necrosis Factor α (TNFα) is a key initiator of brain insulin resistance (Bomfim et al., 2012; De Felice et al., 2014; De Felice and Ferreira, 2014a, 2014b; Lourenco et al., 2013). The 3xTgAD mice exhibit increased TNFα expression in the hypothalamus (Do et al., 2018). AβO-injected mice also show enhanced activation of the TNFα pathway in the hypothalamus, with increased levels of phosphorylated IκB kinase (IKKβ), decreased levels of the nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha (IκBα) and translocation of the nuclear factor kappa B (NFκB) into the nucleus (Clarke et al., 2015). Corroborating the link between inflammation and insulin resistance, the administration of an antibody that neutralizes TNFα, infliximab, blocked the increase in IRS-1 phosphorylated in serine 636 in hippocampal neurons (Bomfim et al., 2012) and prevented memory impairment in mice triggered by AβOs (Lourenco et al., 2013). Moreover, the effects of AβOs on IRS-1 levels were not observed in mice lacking the TNFα type 1 receptor (TNFR1-/-) (Clarke et al., 2015; Lourenco et al., 2013). AβOs also failed to induce glucose intolerance and increase hypothalamic pIKKβ in TNFR1-/- mice, which suggests a role for TNFα in mediating insulin resistance and metabolic alterations induced by AβOs in mice. In addition to the AβO-injected mouse model, the neutralization of TNFα levels by infliximab improved glucose tolerance in APP/PS1 mice (Clarke et al., 2015). This data supports the hypothesis that TNFα is involved in the mechanisms affecting insulin signaling, memory decline and metabolic alterations in AD.

In addition to TNFα, other cytokines might be involved in the induction of insulin resistance in AD. Increased expression of interleukin-1β (IL1β) and interleukin-6 (IL6) was reported in the cortex of human AD patients (Strauss et al., 1992; Taylor et al., 2014) and elevated plasma levels of IL6 and/or IL1 positively correlate with insulin resistance in human population studies (Hu et al., 2004; Pradhan et al., 2001; Spranger et al., 2003; Vozarova et al., 2001). Although IL6 and IL1β are known to induce insulin resistance in peripheral cells (Hoene and Weigert, 2007; Jager et al., 2007; Nov et al., 2010; Senn et al., 2002), studies have shown both protective and detrimental effects of these cytokines in AD. Therefore, it remains to be determined the precise contribution of these cytokines to the induction of insulin resistance in AD. A comparative study using 118 research articles published between 1989 and 2013, corroborated the controversial and inconclusive results obtained in studies investigating cytokines in AD. However, the authors suggested a model of temporal changes of cytokines in the CSF and blood of AD patients, which included IL6, IL1β and TNFα as cytokines that increase slightly, slowly and steadily during disease progression (Brosseron et al., 2014). Longitudinal studies investigating cytokine expression in AD, and how it precisely contributes to insulin resistance, are critically needed to understand the link between inflammation and insulin resistance in AD pathogenesis.

3.2. Endoplasmic reticulum stress

Endoplasmic reticulum (ER) stress is characterized by the accumulation of misfolded proteins in the lumen of the ER and by the activation of unfolded protein response (UPR) pathways. If persistently activated, UPR promotes cell death via apoptosis and mitochondrial dysfunction (Morishima et al., 2004). ER stress can be either a consequence of impaired insulin signaling in the brain or an initiator of insulin resistance in different cell types. The latter concept has been especially investigated in peripheral tissues in the context of obesity and diabetes (Birkenfeld et al., 2011; Koo et al., 2012; Liang et al., 2015; Ozcan et al., 2004; Suzuki et al., 2017).

A variety of ER stress markers are upregulated in the hippocampus and/or cortex of different transgenic AD mouse models (Hashimoto and Saido, 2018), and in the hippocampus (Lourenco et al., 2013) and hypothalamus (Clarke et al., 2015) of the non-transgenic AβO-injected mouse. The link between ER stress and insulin signaling in AD models was first elucidated by findings showing that the Protein kinase RNA-activated (PKR) - a critical component that responds to ER stress in peripheral tissue (Hotamisligil, 2010) - mediates neuronal IRS-1 inhibition induced by AβOs in mice (Bomfim et al., 2012). Moreover, the deletion of PKR reduced the levels of inhibitory IRS-1 phosphorylated in serine 636 in mouse hippocampal homogenates (Lourenco et al., 2013). The blockage of ER stress through icv injections of the chemical chaperone tauroursodeoxycholic acid (TUDCA) (Uppala et al., 2017), attenuated glucose intolerance induced by AβOs in mice (Clarke et al.,

2015). Therefore, considering that impaired hypothalamic insulin signaling leads to glucose intolerance and is a feature of AβO-injected mice (Clarke et al., 2015; Cnop et al., 2012), it is possible that the attenuation of ER stress by TUDCA had a positive effect on glucose homeostasis due to changes in hypothalamic insulin signaling. This corroborates the hypothesis that ER stress is directly linked to impaired insulin signaling in this model, but this idea remains to be investigated in other experimental mouse models of AD.

ER stress is one of the mechanisms linking inflammation to impaired insulin signaling in the brain. Moreover, ER stress can both be the cause (Zhang and Kaufman, 2008) and the consequence of the inflammatory process (Denis et al., 2010; Milanski et al., 2009; Salminen et al., 2009). Therefore, considering the already discussed ability of inflammation to impair insulin signaling, ER stress, inflammation and insulin resistance might be key interconnected events with important roles in the pathogenesis of AD. Collectively, the findings above suggest that ER stress can be an important mediator of impaired brain insulin signaling in AD that will act in synergy with pro-inflammatory signals to trigger cognitive impairment in the disease (Fig. 1).

4. The importance of developing a non-human primate model of Alzheimer`s Disease

The vast majority of AD research has been conducted in rodents, especially transgenic mice. However, there are AD features that rodent models have not been effective at modelling, particularly the development of neurofibrillary tangles, which are only observed in models with an additional tau transgene that is not part of the normal AD pathology (Chabrier et al., 2012; Cohen et al., 2013; Götz et al., 2001; Mcgowan et al., 2006; Oddo et al., 2003). Further, AD involves not only impairment of memory, but also of higher cognitive functions, including planning for future actions, problem solving, judgement and decision making, thinking back in time, and complex social communication (Ballard et al., 2011; Godefroy et al., 2018; McKhann et al., 1984, 2011). These functions are predominantly subserved by neocortical networks in humans, and AD is a prototypical cortical dementia. Rodents not only lack some of the behavioral repertoire of humans, they have lissencephalic brains and lack development of many of the neocortical areas humans use for these cognitive behaviors, in particular they have comparatively little visual and prefrontal cortex. The last common ancestor humans shared with rodents was 75 million years ago (MYA), and dramatic changes in brain structure and function occurred during primate evolution: primate brains became more specialized for vision and less so for olfaction, and there was a massive expansion of neocortex in general and prefrontal cortex in particular (Kaas, 2013).

Humans and old world monkeys such as macaques diverged only 25-30 MYA (Kaas, 2005). Because human and NHP brains share similarities in overall architecture and organization of functional networks, and NHPs can be trained to perform many of the cognitive tasks used in human clinical studies, the strategy of validating NHP model of AD has the potential to greatly advance our understanding of mechanisms centrally implicated in AD pathogenesis and effective therapeutic development.

Two types of NHP models involving macaques are under investigation (Van Dam and De Deyn, 2017) – natural aging models (Chen et al., 2018; Cramer et al., 2018; Darusman et al., 2014; Latimer et al., 2018; Lemere et al., 2008) and inducible models (e.g., Forny-Germano et al., 2014). While natural aging models show some promise because they exhibit amyloidosis and tau phosphorylation, they do not typically show tangle pathology. Furthermore, they are limited by the fact that animals must be aged and not all animals that reach old age will actually show features of the disease. This would make clinical testing of therapeutics inefficient.

With the goal of bridging the gap between the rodent models and patients, our group has been developing an inducible NHP model of AD. Due to an extensive literature showing that AβOs may act as central toxins in AD (Bomfim et al., 2012; Clarke et al., 2015; Gong et al., 2003; Lourenco et al., 2013) our NHP model (AβO-injected NHPs) consists of icv injections of AβOs in cynomolgus macaques (Forny-Germano et al., 2014). Upon icv injection, the AβOs were found to distribute widely in the NHPs brain parenchyma; binding mostly to cells with neuronal morphology in several brain regions, including the entorhinal, frontal and parietal cortices, as well as the hippocampus and the hypothalamus (Clarke et al., 2015; Forny-Germano et al., 2014).

5. Insulin resistance in a non-human primate model of Alzheimer`s Disease

Altered cellular distribution and decreased tyrosine phosphorylation of the insulin receptor (IR), and elevated IRS-1 phosphorylation at serine residues are some of the markers of defective insulin signaling reported in the brains of AD patients (Bomfim et al., 2012; Moloney et al., 2010; Talbot et al., 2012). Remarkably, signs of brain insulin resistance were detected in neuronal-derived extracellular vesicles enriched from the blood of AD patients, which have increased levels of phospho-serine 312 and decreased phospho-pan-tyrosine IRS-1 levels (Kapogiannis et al., 2015). Interestingly, the insulin signaling activation status correlated negatively with measurements of episodic memory in AD patients, indicating that insulin resistance may underlie cognitive decline in this condition (Talbot et al., 2012). Analyses of NHP brains demonstrated that AβOs triggered the loss of IRα and IRβ subunits in the frontal cortex, hippocampus and amygdala, as well as increased IRS-1 phosphorylated in serine 636 in the hippocampus (Batista et al., 2018; Bomfim et al., 2012). Overall, AβOs induced the activation of stress pathways and defective insulin signaling in the brains of NHPs, which resembles what has been observed in AD patients. The results obtained in AβO-injected NHPs suggest that the overproduction of Aβ in the human brain may underlie impaired neuronal insulin signaling in early stages of the disease, culminating in memory decline in more advanced stages.

Type 2 diabetes (T2D) medications that boost insulin signaling can bypass the IR and reduce insulin resistance (Ozcan et al., 2006; Saltiel and Olefsky, 1996). Analogs of glucagon-like peptide-1 receptor (GLP-1R), such as liraglutide and exendin-4, restored insulin signaling in T2D (Drucker, 2003; Hölscher, 2014) and exhibited promising results in biochemical and behavioral measures when tested in rodent models of AD (Bomfim et al., 2012; Hölscher, 2014; McClean et al., 2011; McClean and Hölscher, 2014). In humans, clinical trials are currently being conducted to assess if liraglutide can improve cognitive and/or positron emission tomography (PET) and CSF biomarkers in AD patients (NCT01469351, NCT01843075). The success of GLP-1R analogs in different AD rodent models and the possible translation to humans as a therapeutic strategy, prompted our group to develop a follow-up study involving pre-treatment of AβO-injected NHPs with liraglutide. We hypothesized that the promotion of insulin signaling pathway could protect NHP brains from the deleterious cascade initiated by the injection of AβOs. Histological analysis carried out in the frontal cortex, hippocampus and amygdala of these animals demonstrated that liraglutide could prevent IRα and IRβ subunits loss and attenuate synapse shrinkage and AβO-induced phosphorylated tau (Batista et al., 2018). Results obtained in mice and in hippocampal cultures indicated that the protective effect of liraglutide was at the IR mRNA level and involved the activation of the cAMP/PKA pathway (Batista et al., 2018).

Inflammation is a double-edged sword in AD, although it may confer neuroprotection in the earlier stages of the disease (Parkhurst et al., 2013), a continuous imbalance of the neuroinflammatory response can disrupt proper neuronal function and contribute to AD pathogenesis (Heneka et al., 2015b; Mawuenyega et al., 2010). Astrocytes and microglia accumulate around Aβ plaques in AD brains (Condello et al., 2015; Farfara et al., 2008). Our NHP model of AD recapitulated some of these pathological characteristics with increased glial fibrillary acidic protein (GFAP) and ionized calcium-binding adapter molecule 1

(IBA-1) staining, indicating astrocytic and microglial mobilization in the frontal cortex, hippocampus and amygdala (Forny-Germano et al., 2014). We also observed that the hypothalamus of the AβO-injected NHPs had higher phosphorylated IKKβ and lower IκBα immunostaining (Clarke et al., 2015), reinforcing the idea that the TNFα pathway might be activated in the primate brain.

Elevated phosphorylated PKR (pPKR) staining is observed in the brains of AD patients (Bose et al., 2011; Hugon et al., 2017) and high pPKR CSF levels predicted poorer performance on the Mini-Mental State Examination (MMSE) (Dumurgier et al., 2013). Interestingly, similar to what is observed in AD, the hippocampus and the entorhinal cortex of AβO-injected NHPs have increased pPKR staining (Lourenco et al., 2013). The phosphorylation of IKKβ and PKR, kinases involved with IRS-1 phosphorylation in serine residues, may be a mechanism by which the accumulation of AβOs could trigger insulin resistance in the primate brain (Fig. 1).

As previously discussed, ER stress can lead to defective insulin signaling promoted by the activation of specific kinases of the UPR and c-Jun N-terminal kinase (JNK) activation (Hotamisligil, 2008). Evidence of UPR activation and elevated protein levels of total and activated forms of JNK are observed in AD brains (Montibeller and de Belleroche, 2018; X Zhu et al., 2001a). In particular, phosphorylation of eukaryotic initiation factor 2α (eiF2α) occurs in the hippocampus of AD patients and activated protein kinase RNA-like endoplasmic reticulum kinase (PERK), a kinase that phosphorylates eiF2α, co-localizes with neurofibrillary tangles in tauopathies (Nijholt et al., 2012). Similar results are seen in AβO-injected NHPs: analysis of phosphorylated eIF2α (peiF2α) and JNK in the hippocampus and entorhinal cortex demonstrated activation of this pathway, suggesting that increased levels of AβOs promote ER stress in the primate brain, as well as the activation of the UPR response (Bomfim et al., 2012; Lourenco et al., 2013). As described above, PKR is also upregulated in AD and is involved with eiF2α phosphorylation (Hugon et al., 2017; Taylor et al., 2005), providing a possible mechanism for the increase in peiF2α levels. In NHPs, liraglutide prevented the increase of peIF2α in the same brain regions, indicating that ameliorating intracellular insulin signaling would prevent ER stress (Lourenco et al., 2013) (Fig. 1). Importantly, the hypothalamus also exhibits more peIF2α staining (Clarke et al., 2015), suggesting that the AβOs promote hypothalamic ER stress, a phenomenon shown to be pivotal for the peripheral metabolic control in mice (Zhang et al., 2008) (Fig. 2).

5.1. Synapse loss

The severity of cognitive decline correlates well with synapse loss in AD (DeKosky and Scheff, 1990; Scheff and Price, 1993; Terry et al., 1991). Electron micrographs shown decreased synapse density in the AD hippocampus (Neuman et al., 2015). Synaptophysin is a protein present in the pre-synaptic vesicles, that is used as a marker of synapse density (Masliah et al., 1990; Tarsa and Goda, 2002; Wiedenmann and Franke, 1985). The midfrontal and inferior parietal regions of AD patients have 40% loss of synapthophysin immunoreactivity, which correlates with MMSE scores (Terry et al., 1991). Similar to what is observed in human brains, AβO-injected NHPs have decreased levels of synaptophysin immunostaining in cognitive-related brain areas and 15% loss of synapse number in the frontal cortex. The postsynaptic density-95 protein (PSD-95) is a scaffold protein that participates in receptor anchorage and trafficking in the post-synapse (Bredt and Nicoll, 2003; Harris and Weinberg, 2012). Reduced levels of PSD-95 (co-localized with synaptophysin) were observed in the frontal cortex, hippocampus and amygdala of AβO-injected NHPs (Batista et al., 2018; Forny-Germano et al., 2014). In the AD brain, reductions of PSD-95 levels have also been observed in the hippocampus (Counts et al., 2014). On the other hand, specific layers of cortical areas have aberrant expression of PSD-95 suggesting differential susceptibility, and/or compensation, that could culminate in altered cognitive behavior (Savioz et al., 2014). Importantly, liraglutide prevented some of the decrease in synapse number caused by AβOs in the brains of NHPs (Batista et al., 2018). Also, peIF2α promotes synapse loss, demonstrated by the downregulation of synaptophysin and PSD-95 (Lourenco et al., 2013). The fact that liraglutide restored peIF2α in the NHPs brains and the role of eIF2α on protein translation indicate the involvement of ER stress impacting synapse density in the AD brain (Ma et al., 2013; Martínez et al., 2016; Ohno, 2014) (Fig. 1).

5.2. Tau pathology

Tau pathology is a major, well stablished hallmark of AD brains (Braak and Braak, 1997; Braak and Del Tredici, 2018; Gómez-Isla et al., 1997; Hyman et al., 1984). Transgenic mouse models of AD usually have mutations in the amyloid precursor protein (APP) and presenilin 1 (PS1) genes linked to familial forms of AD. As described previously, those animals replicate important features of AD, but the development of neurofibrillary tangles are only observed upon the insertion of tau transgenes, that carry mutations observed in tauopathies, but not in AD (De Felice and Munoz, 2016; Oddo et al., 2003). In contrast to rodents, some NHPs naturally develop age-dependent amyloid insoluble deposits and neurofibrillary tangles (Heuer et al., 2012; Oikawa et al., 2010). In cynomolgus macaques, phosphorylated tau was detected at approximately 20 years of age, prior to the detection of insoluble Aβ in the neocortex and hippocampus, while tangles were only detected in advanced ages, over 30 years-old (Oikawa et al., 2010). Our AβO-injected macaques ranged in age from 9 to 16 years-old, before any natural appearance of insoluble plaques, hyperphosphorylated tau or neurofibrillary tangles might occur. Interestingly, we observed that the injection of AβOs promoted tau phosphorylation and remarkably, neurofibrillary tangles, years before these features could emerge by natural processes. The presence of neurofibrillary tangles was confirmed using several epitope-specific and conformational antibodies and by electron microscopy analyses (Forny-Germano et al., 2014).

According to previous results showing the absence of insoluble structures in the brain of young adult cynomolgus macaques, no Thioflavin-S (ThioS) staining was detected in the frontal cortex of a sham operated animal. Meanwhile, an AβO-injected NHP exhibited intracellular positive ThioS staining throughout the cortical layers (Fig. 3). Of relevance, the detection of tangle-like structures was more prominent at layer II of the frontal cortex (Fig. 3). Interestingly, the superficial cortical layers of humans are more susceptible to neurodegeneration in AD (Gómez-Isla et al., 1996; Romito-DiGiacomo et al., 2007) indicating a possible valuable similarity between humans and NHPs. Despite the presence of neurofibrillary tangles, no evidence of cell-death were observed in the frontal cortex of the AβO-injected NHPs indicating that this model replicates stages of AD that precede neurodegeneration (Forny-Germano et al., 2014).

Development of neurofibrillary tangles follows a similar progression to activation of JNK in AD brain regions (Sato et al., 2002; Shoji et al., 2000; Zhu et al., 2001a). In AD models, JNK was shown to be involved with tau phosphorylation at serine 202/threonine 205 residues, which is recognized by the AT8 antibody (Braak et al., 2006; Ploia et al., 2011). GSK3β is a tau kinase, that is activated by PKR and negatively regulated by insulin (Sperber et al., 1995; Zhu et al., 2018). Interestingly, PKR co-localizes with both GSK3β and AT8 staining in neurons of AD human brains (Bose et al., 2011). The elevated levels of AT8 in the frontal cortex of the AβO-injected NHPs (Forny-Germano et al., 2014) indicate a possible involvement of JNK, PKR and GSK3β mediating tau hyperphosphorylation elicited by the AβOs in the primate brain (Nijholt et al., 2012) (Fig. 1).

Tau is able to inhibit the phosphatase and tensin homolog (PTEN), involved with the dephosphorylation of PIP_3 (Marciniak et al., 2017) (Fig. 1), which leads to the hypothesis that, in AD, tau hyperphosphorylation and aggregation into neurofibrillary tangles would characterize its loss-of-function promoting insulin signaling impairments

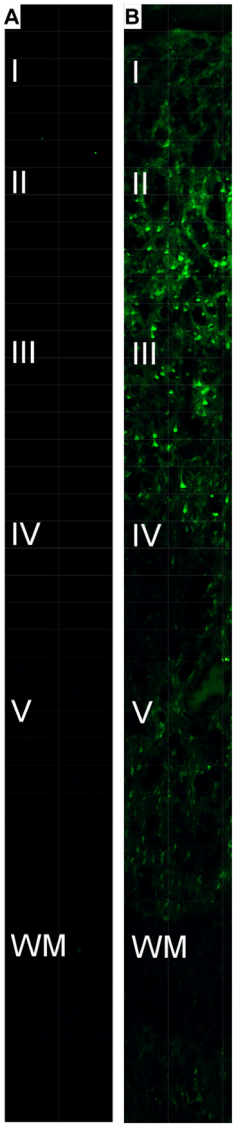

Fig. 3. Intracellular thioflavin-S positive cells are more prominent at cortical layer 2 of an AβO-injected NHP. Photomicrographs of the frontal cortical layers (I-V) of a sham operated and an AβO-injected NHPs stained for thioflavin-S. No staining was detected in the sham operated animal. WM: white matter.

(Gratuze and Planel, 2017). This hypothesis is supported by publications showing defective central and peripheral insulin signaling in Tau knockout mice (Marciniak et al., 2017; Wijesekara et al., 2017). Moreover, in cultures, hyperphosphorylation of tau triggers insulin oligomerization and, the accumulation of oligomerized forms of insulin occurs in neurons exhibiting neurofibrillary tangles in the brains of AD patients (Rodriguez-Rodriguez et al., 2017). *In vitro*, the overexpression of a truncated form of tau elicits insulin signaling impairment (Guo et al., 2019). Altogether, these results indicate that tau could act as a major player mediating insulin resistance in the AD brain.

Remarkably, liraglutide attenuated tau phosphorylation in AβO-injected NHPs indicating that strategies designed to restore the insulin signaling pathway can ameliorate AD pathology (Batista et al., 2018). We believe that an animal model that resembles all pathogenic aspects of AD, including insulin signaling impairment and neurofibrillary tangles, would be of significant benefit to research for therapeutics in AD.

6. Conclusion

Cumulative data indicate that insulin signaling declines in AD brains, a feature that has been replicated in various rodent models and in an inducible model of AD in NHPs. The mechanisms underlying impairment of insulin signaling are yet to be fully unraveled. Here, we have provided an overview of cellular mechanisms that may prompt insulin signaling dysfunction in the brains of AD patients, which includes inflammation and ER stress. We also argued that due to the greater similarity between NHP and human brains, the NHP model is valuable for examining disease mechanisms and therefore might be of great relevance to human translation.

Author contribution statement

NLS: Development of the subject matter, drafting of the article, conception and design of the figures, critical revision of the article, final approval of the version to be published; RG: Development of the subject matter, drafting of the article, critical revision of the article, final approval of the version to be published; SB: Development of the subject matter, drafting of the article, critical revision of the article, final approval of the version to be published; LFG: Critical revision of the article, final approval of the version to be published; DM and FDF: Development of the subject matter, drafting of the article, critical revision of the article, final approval of the version to be published.

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