

Brain metabolic stress and neuroinflammation at the basis of cognitive impairment in Alzheimer's disease

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Brain metabolic dysfunction is known to influence brain activity in several neurological disorders, including Alzheimer's disease (AD). In fact, deregulation of neuronal metabolism has been postulated to play a key role leading to the clinical outcomes observed in AD. Besides deficits in glucose utilization in AD patients, recent evidence has implicated neuroinflammation and endoplasmic reticulum (ER) stress as components of a novel form of brain metabolic stress that develop in AD and other neurological disorders. Here we review findings supporting this novel paradigm and further discuss how these mechanisms seem to participate in synapse and cognitive impairments that are germane to AD. These deleterious processes resemble pathways that act in peripheral tissues leading to insulin resistance and glucose intolerance, in an intriguing molecular connection linking AD to diabetes. The discovery of detailed mechanisms leading to neuronal metabolic stress may be a key step that will allow the understanding how cognitive impairment develops in AD, thereby offering new avenues for effective disease prevention and therapeutic targeting.

Keywords: Alzheimer's disease, amyloid- β oligomers, endoplasmic reticulum stress, inflammation, metabolic stress

Introduction

Incidence of Alzheimer's disease (AD) will greatly increase as world population ages (Prince et al., 2013) and changes in lifestyle observed in recent decades seem to be major contributors to such increased prevalence (Mattson, 2012; De Felice, 2013). Likewise, common diseases of modern adulthood, including obesity and diabetes mellitus, have been often regarded as AD risk factors (De Felice, 2013). Pioneering epidemiological studies connecting AD to diabetes initiated in the 1990s (Ott et al., 1996, 1999; Kalmijin et al., 1997) and were followed by several reports providing both clinical and experimental evidence into how these two disorders may course together (de la Monte, 2009; Matsuzaki et al., 2010; Crane et al., 2013; De Felice, 2013; De Felice et al., 2014).

Metabolic derangements, including inflammation, insulin resistance and endoplasmic reticulum (ER) stress, are known to underlie glucose intolerance and type 2 diabetes mellitus (T2DM) in peripheral tissues (Hotamisligil et al., 1995, 1996; Ozcan et al., 2004, 2006; Hotamisligil, 2006). A similar scenario has been recently described in the brains of patients that suffer from neurodegenerative disorders, such as AD. Neuropathology investigations have revealed that AD brains present several markers of insulin resistance, inflammation and ER stress (Hoozemans et al., 2005; Steen et al., 2005; Moloney et al., 2010; Bomfim et al., 2012; Talbot et al., 2012; O'Neill, 2013;

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De Felice et al., 2014). In the following sections, we review current evidence indicating that a newly defined form of metabolic stress leads the path to cognitive decline in AD. The understanding of molecular mechanisms driving AD pathogenesis may shed new light on novel targets for drug development and offer strategies for disease prevention.

AD Pathogenesis

AD pathophysiology includes neuroinflammation, oxidative and ER stress, synapse loss and degeneration of specific neuronal populations (Selkoe, 2002; Ferreira and Klein, 2011; Mucke and Selkoe, 2012). Amyloid- β peptide ($A\beta$) is the main component of senile plaques that accumulate in AD brains (Masters et al., 1985), and substantial evidence indicates that $A\beta$ is causally involved in AD (Mucke and Selkoe, 2012). Consolidated knowledge has established that soluble $A\beta$ oligomers ($A\beta$ Os; Lambert et al., 1998), and not necessarily the insoluble amyloid fibrils detected in senile plaques, promote direct damage to synapses, besides stimulating inflammatory response and cellular stress (Ferreira and Klein, 2011; Viola and Klein, 2015). These findings prompt $A\beta$ Os, which are increased in AD brains (Gong et al., 2003; Xia et al., 2009), to be considered neurotoxins responsible for synapse and memory loss in AD early stages.

Very recent data has demonstrated that $A\beta$ O actions stimulate pro-inflammatory mechanisms to impair neuronal insulin signaling and to trigger stress kinase activation, resulting in synapse and memory impairments in AD models (Bomfim et al., 2012; Lourenco et al., 2013; Ma et al., 2013). These events are quite similar to those acting in peripheral tissues to impair metabolism in diabetes and obesity (De Felice and Ferreira, 2014), in line with the idea that a form of metabolic stress develops in AD brains (Kapogiannis and Mattson, 2011; Yoon et al., 2012; De Felice and Ferreira, 2014). Such findings may impact translational research, as treating brain metabolic dysfunction might be a key strategy to fight neurological disorders.

Brain Metabolic Stress Mechanisms in AD

In peripheral tissues, prolonged inflammatory cascades lead to the activation of multiple cellular stress mechanisms that ultimately impair cell function and body metabolism (Hotamisligil, 2006; Gregor and Hotamisligil, 2011). In AD, evidence arising from *in vitro*, *in vivo* and neuropathology studies supports that such events occur throughout disease development and are linked to $A\beta$ O neurotoxicity. Oligomers promote neuronal stress by instigating abnormal elevations in levels of tumor necrosis factor α (TNF- α) and reactive oxygen species (ROS), as well as activation in JNK/PKR signaling and increased eIF2 α phosphorylation (eIF2 α -P) levels in AD models (De Felice et al., 2007, 2014; Ma et al., 2009, 2013; Bomfim et al., 2012; Lourenco et al., 2013). In this context, pro-inflammatory signals appear to be directly responsible for defective insulin signaling and stress-mediated synapse loss caused by $A\beta$ Os in neurons (Bomfim et al., 2012; Lourenco

et al., 2013). This has led to a concept in which $A\beta$ Os build up in pre-AD brains to cause inflammation (e.g., gliosis and cytokine production) and neuronal metabolic stress, ultimately leading to synaptic dysfunction and behavioral alterations. We next detail some of the mechanisms recently implicated in AD pathogenesis.

Unfolded Protein Response

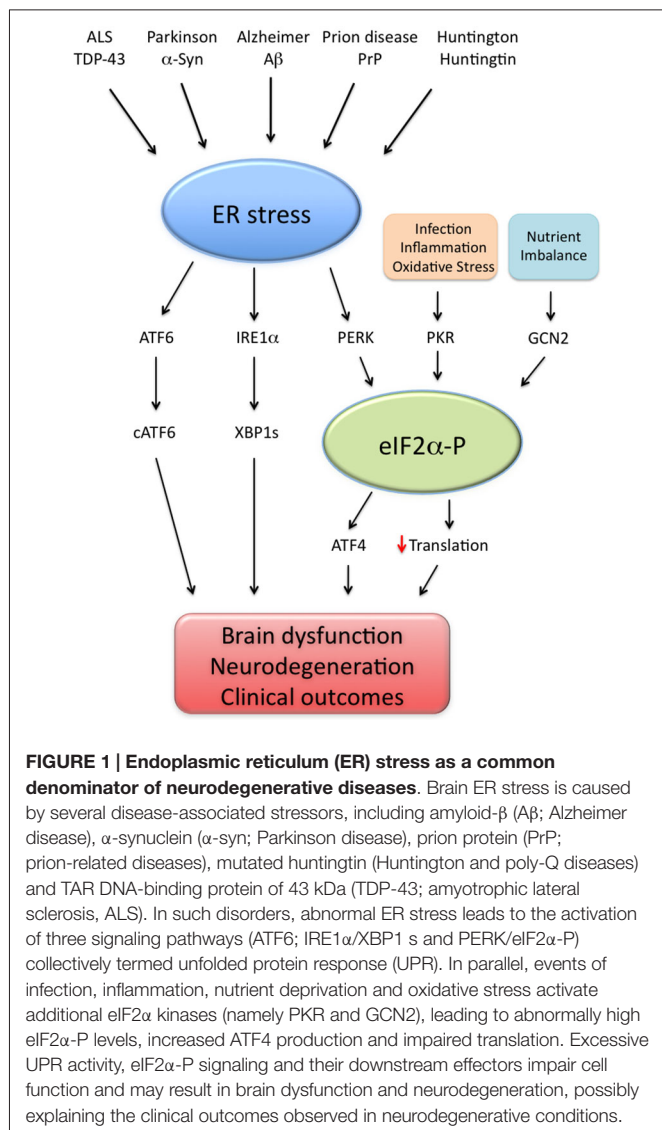
Unfolded Protein Response (UPR) is defined as a collection of signaling pathways that respond to ER stress due to accumulation of misfolded proteins and/or impaired homeostasis. ER membrane sensors activate three signaling axes (ATF6 α , IRE-1 α /XBP-1s and PERK/eIF2 α -P) to instigate transcriptional and translational alterations aimed at restoring cell homeostasis (Lai et al., 2007; Hetz et al., 2013). UPR signaling attenuates global translation and favors the synthesis of select transcription factors, such as ATF4, CHOP and Nrf2 (Buffington et al., 2014; Hetz and Mollereau, 2014). Under continued stress, however, these pathways may promote cell damage and death. This hormetic response pattern is thus critical to determine cell fate in such conditions (Mattson, 2008; Hetz, 2012).

Evidence for canonical UPR activation has been found in AD neurons (Hoozemans et al., 2005, 2009; Yoon et al., 2012) and in AD mouse models (Yoon et al., 2012; Ma et al., 2013). In accordance, $A\beta$ Os trigger UPR in hippocampal neurons *in vitro* and *in vivo* (Chafekar et al., 2007; Casas-Tinto et al., 2011; Lourenco et al., 2013; Barbero-Camps et al., 2014), and experimental induction of ER stress leads to neuronal metabolic stress (Yoon et al., 2012), tau phosphorylation (Bose et al., 2011; van der Harg et al., 2014), stress kinase activation (Bose et al., 2011; Paquet et al., 2011) and cognitive impairment in mice (Lourenco et al., 2013). Further, alleviating ER stress with 4-phenylbutyrate, a chemical chaperone, promotes cognitive benefits in AD mouse models (Ricobaraza et al., 2009, 2010; Wiley et al., 2011; Lourenco et al., 2013).

Substantial recent evidence has proposed that UPR activation is a common feature of different neurodegenerative diseases, as deleterious impacts of UPR branches were reported in AD (Lourenco et al., 2013; Ma et al., 2013; Barbero-Camps et al., 2014; van der Harg et al., 2014), Parkinson's (Bellucci et al., 2011; Colla et al., 2012), Huntington (Lajole and Snapp, 2011), amyotrophic lateral sclerosis (ALS; Hetz et al., 2009; Kim et al., 2013) and prion diseases (Moreno et al., 2012). Correcting UPR activation further appears to be effective in preclinical models of prion infection (Moreno et al., 2012, 2013; Halliday et al., 2015) and ALS (Hetz et al., 2009; Kim et al., 2013), in addition to AD models (Ricobaraza et al., 2009, 2010; Lourenco et al., 2013; Ma et al., 2013). Therefore, it is likely that aberrant UPR signaling mediates brain dysfunction in a variety of neurological conditions (Figure 1).

eIF2 α -P and Translational Repression

Under cellular stress, translational repression can be mediated by increased eIF2 α phosphorylation (eIF2 α -P), a regulatory factor essential for translation initiation in eukaryotes (Raven and Koromilas, 2008). PERK-mediated eIF2 α -P is the main UPR branch leading to general protein synthesis repression and



facilitation of select mRNA translation (Buffington et al., 2014). Both PERK and eIF2 α -P appear to be elevated in AD brains (Chang et al., 2002b; Yoon et al., 2012; Ma et al., 2013) and are induced by $A\beta$ aggregates in neurons (Lee et al., 2010). Increased eIF2 α -P has been further verified in other AD mouse models (Segev et al., 2012; Devi and Ohno, 2014).

Two other eIF2 α kinases, namely the stress kinase PKR and the nutrient sensor GCN2, are enriched in the brain and have been reported to increase neuronal eIF2 α -P (Costa-Mattioli et al., 2005; Lourenco et al., 2013; Roffé et al., 2013; Hetz and Mollereau, 2014), and thus emerge as candidates to explain increased eIF2 α -P in AD.

Interestingly, deletion of either PERK or GCN2 in the brains of APP/PS1 mice decreases eIF2 α -P levels, rescuing synapse plasticity and cognition (Ma et al., 2013). $A\beta$ Os increase eIF2 α -P through TNF- α -dependent PKR activation, thereby promoting synapse loss in hippocampal neurons and cognitive impairment in mice (Paquet et al., 2011; Lourenco et al., 2013). Providing

clinical relevance to the findings observed in experimental models, PKR was found to be abnormally active in AD brains (Chang et al., 2002a; Paquet et al., 2011; Mouton-Liger et al., 2012b). Therefore, it is likely that PERK, GCN2, and PKR lead to increased eIF2 α -P levels in AD.

Increased eIF2 α -P levels also facilitate the translation of a small fraction of mRNAs (Buffington et al., 2014), among which is activating transcription factor 4 (ATF4), a protein linked to oxidative stress, enhanced γ -secretase activity and neuronal dysfunction when abnormally elevated (Mitsuda et al., 2007; Lange et al., 2008). ATF4 signaling further counteracts CREB1 pro-memory actions in mice (Costa-Mattioli et al., 2005; Rajasethupathy et al., 2012).

Recent findings demonstrated that ATF4 levels are increased in AD brains (Yoon et al., 2012; Baleriola et al., 2014) and in AD animal models (Ma et al., 2013; Devi and Ohno, 2014). Furthermore, soluble $A\beta$ species appear to locally stimulate axonal ATF4 translation to propagate a neurodegenerative message in mice (Baleriola et al., 2014). Hence, eIF2 α -P/ATF4 signaling has the potential to explain, at least in part, how disease progresses from defined brain regions in the beginning to a widespread forebrain dysfunction at later stages.

Translational repression instigated by eIF2 α -P may be harmful to cognition, given that normal protein synthesis is required for memory (Flexner et al., 1964; Rossato et al., 2007). Accordingly, APP/PS1 mice present reduced brain protein synthesis in parallel to memory loss, and $A\beta$ Os impair LTP-induced hippocampal protein synthesis (Ma et al., 2013). Nevertheless, the identity of memory-relevant translational products that are impacted in AD still remains to be determined.

Stress Kinase Activation

Cellular stress is also known to activate a family of protein kinases that mediate adaptive responses (Calay and Hotamisligil, 2013). These proteins are termed stress-sensitive kinases (or simply stress kinases) and include JNK, p38 MAPK, PKR, PERK and IKK, among other serine/threonine kinases (Vallerie and Hotamisligil, 2010; Hetz and Mollereau, 2014). Active stress kinases phosphorylate several protein targets to restore homeostasis. Nevertheless, their excessive or prolonged actions may trigger cell injury and, later, programmed cell death (Mattson, 2008; Vallerie and Hotamisligil, 2010; Hetz, 2012; De Felice et al., 2014).

Neuropathology studies have demonstrated abnormal activation of neuronal stress-sensitive kinases in AD brains. Indeed, abnormal phosphorylation of p38 MAPK (Hensley et al., 1999), JNK (Ma et al., 2009; Bomfim et al., 2012; Yoon et al., 2012), PERK (Hoozemans et al., 2005, 2009), PKR (Chang et al., 2002a; Paquet et al., 2011) and IKK (Talbot et al., 2012) have been reported in AD brains and might be core mediators of neuronal dysfunction. Accordingly, $A\beta$ Os have been described to activate neuronal JNK and PKR to impair insulin signaling and synapse function (Ma et al., 2009; Bomfim et al., 2012; Lourenco et al., 2013), and transgenic animal models of AD exhibit similar alterations in JNK and PKR activity (Ma et al., 2009; Bomfim et al., 2012; Lourenco et al., 2013). Consistently,

blocking either PKR or the brain-enriched JNK3 rescue cognitive impairments in AD mouse models (Yoon et al., 2012; Lourenco et al., 2013), suggesting that stress kinase activation lies upstream of synapse and memory impairment in AD.

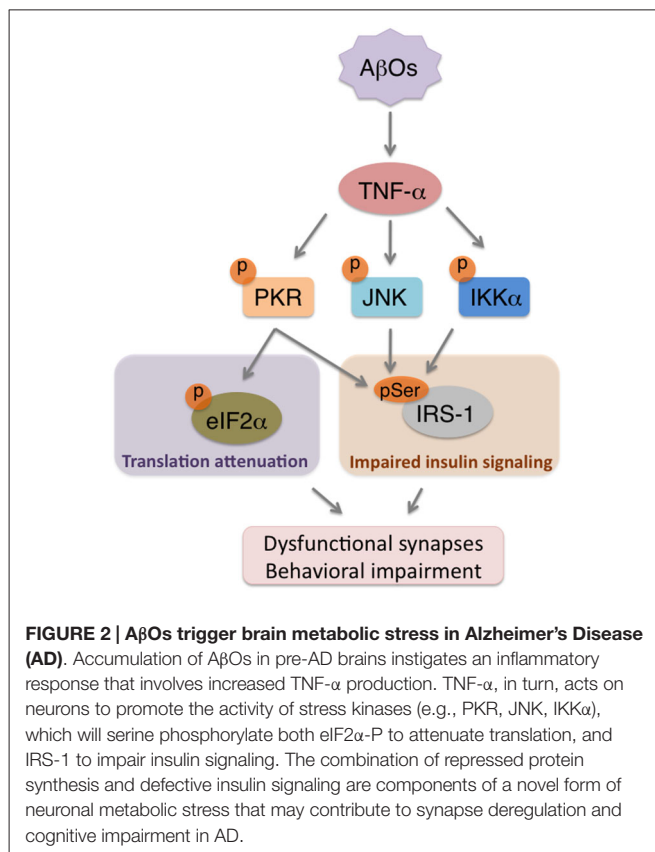
An attractive possibility is that PKR further drives the activation of other MAPKs, such as p38MAPK and JNK, thus exacerbating neuronal damage. Very recent findings suggest that the interaction between PKR and the RNA-binding protein TRBP is essential to promote eIF2 α -P and JNK activation under obesity-induced metabolic stress (Nakamura et al., 2015). A similar scenario might also develop in AD even independently of TNF- α , given that oxidative stress has been reported to activate neuronal PKR (Mouton-Liger et al., 2012a). Moreover, A β Os could activate PKR in glial cells to instigate MAPK-dependent actions, exacerbating neuroinflammatory responses in AD brains. These notions still demand further investigation.

Neuroinflammation

Elevated markers of inflammation are found in both AD animal models and human AD brains (Ferreira et al., 2014; Monson et al., 2014; Heneka et al., 2015). Consistently, evidence for gliosis and central infiltration of peripheral immune cells is often found in histopathological studies in AD mouse models (Yamanaka et al., 2012; Lourenco and Ledo, 2013; Yang et al., 2013; Baik et al., 2014; Ferreira et al., 2014; Monson et al., 2014).

Amyloid aggregates (ranging from oligomers to fibrils) induce a neuroinflammatory profile that may lead to synapse and neuronal damage (Combs, 2009; Pan et al., 2011; Lourenco et al., 2013; Medinas and Hetz, 2013; Parajuli et al., 2013; Heneka et al., 2015). Nevertheless, rather than deposited plaques, A β Os are thought to be core inducers of brain inflammation, given that they are potent microglial activators (Floden and Combs, 2006; Dhawan et al., 2012; Ledo et al., 2013) and diffuse throughout brain regions (Lambert et al., 1998; Forny-Germano et al., 2014; Viola and Klein, 2015). Accumulating evidence suggests that A β O-induced microglial activation releases TNF- α and other cytokines that, in turn, act on neurons to cause stress signaling and synapse injury (Floden and Combs, 2006; Sondag et al., 2009; Bomfim et al., 2012; Dhawan et al., 2012; Lourenco et al., 2013).

Therefore, neuroinflammation is considered to take place over the degenerative course of AD and to be linked to cognitive dysfunction. In fact, our recent results showed that A β O-triggered elevations in TNF- α levels orchestrate neuronal stress mechanisms to impair brain insulin signaling (Bomfim et al., 2012), synapses and cognition in animal models of AD (Lourenco et al., 2013; **Figure 2**). This cascade is mediated by stress kinases, including JNK and PKR, in the brains affected by A β Os (Lourenco et al., 2013). Since evidence suggests that reducing neuroinflammation can counteract memory deficits in AD mouse models (Medeiros et al., 2007; McAlpine et al., 2009; Kiyota et al., 2010; Bachstetter et al., 2012), a more complete understanding of how brain inflammation develops may lead to effective targeting of aberrant mechanisms underlying cognitive symptoms in AD.



Metabolic Stress and Cognitive Function in AD

Experimental evidence has gathered inflammation, defective insulin signaling and cell stress to AD-linked neurotoxicity and neurodegeneration in a revised concept of metabolic stress (Paquet et al., 2011; Mouton-Liger et al., 2012a; Yoon et al., 2012; Ledo et al., 2013; Lourenco et al., 2013; Ma et al., 2013; Baleriola et al., 2014; De Felice et al., 2014). Although the classical alterations in glucose metabolism germane to metabolic impairments are observed in AD brains (Hoyer et al., 1988; Kapogiannis and Mattson, 2011; Chen and Zhong, 2013), the modern notion of metabolic stress also includes disturbances in proteostasis and activation of signaling pathways that mediate cellular stress.

In this context, the progressive build-up of A β Os in AD brains might trigger the activation of immune mechanisms, including glial cell reactivity and cytokine release that, in turn, lead to neuronal metabolic stress. A point of convergence of multiple stress pathways is found on elevated eIF2 α -P levels. Accordingly, PKR, ER stress, eIF2 α -P and ATF4 have been described as negative modulators of memory (Costa-Mattioli et al., 2007; Zhu et al., 2011; Rajasethupathy et al., 2012; Lourenco et al., 2013; Stern et al., 2013; Di Prisco et al., 2014; Ounallah-Saad et al., 2014). By acting together, such pathways might disrupt brain homeostasis and contribute to the cognitive decline observed in AD.

The precise mechanisms linking metabolic stress to synapse defects are still not fully understood, but the findings that increased eIF2 α -P levels lead to LTP impairments (Ma et al., 2013) and synapse loss (Lourenco et al., 2013) in mice have provided initial clues on this causal relationship. Consistently, restoring normal brain eIF2 α -P levels was shown to abrogate deficient levels of synaptic proteins and cognition (Lourenco et al., 2013; Ma et al., 2013), indicating a tight connection between eIF2 α -P and synapse/memory integrity.

It is noteworthy that activation of PKR/eIF2 α -P signaling (O'Connor et al., 2008; Devi and Ohno, 2010; Mouton-Liger et al., 2012a), as well as high-fat diet-induced metabolic stress (Wang et al., 2013) was shown to promote amyloidogenesis in a feed-forward cycle that might exacerbate amyloid pathology. It is thus tempting to speculate that accumulating injuries throughout life, including infections, diabetes and obesity, could instigate a brain metabolic stress scenario that includes ER stress and neuroinflammation to facilitate A β accumulation and sporadic AD onset at later stages of life (Herrup, 2010; Mattson, 2012; De Felice, 2013).

An unresolved question relates to whether brain insulin resistance could itself trigger AD-related phenomena, even in the absence of inflammation. In this regard, early studies using neuronal insulin receptor knockout (NIRKO) mice found that deficient brain insulin signaling causes abnormal tau phosphorylation without spatial memory impairment (Schubert et al., 2004). Recently, NIRKO mice were shown to develop anxiety and depressive-like behavior linked to altered dopamine metabolism (Kleinriders et al., 2015), and deletion of a single gene copy that encodes an insulin receptor subunit in the brain impairs synaptic plasticity and cognition (Nisticò et al., 2012). Nonetheless, it remains to be determined whether such mice develop brain metabolic stress in the presence or absence of neurotoxic stimuli. Future investigation may dissect the molecular steps that are required for metabolic stress-induced synapse impairments in an AD context.

Conclusions

Recent exciting evidence has connected A β O-induced neuronal stress to cognitive impairments in AD, in a mechanism

that includes cytokine-induced activation of stress kinases and ultimately leads to neuronal and synapse dysfunction in AD experimental models (De Felice et al., 2007; Yoon et al., 2012; De Felice, 2013; Lourenco et al., 2013; Ma et al., 2013; Baleriola et al., 2014; De Felice and Ferreira, 2014; Ferreira et al., 2014). Hence, the combination of inflammation, neuronal insulin resistance, oxidative/ER stress and translational repression might generate a noxious scenario of brain metabolic stress to mediate and propagate synapse defects, resulting in cognitive deficits. In this context, ER stress and abnormal eIF2 α -P levels emerged as key players in neuronal damage.

Sporadic AD is largely idiopathic, and it is noteworthy that A β -centric views of AD pathogenesis remain controversial (see Morris et al., 2014 for a critical review). Nonetheless, recent progress summarized here may have deep implications for disease prevention, as avoiding harmful events throughout life might reduce the risk of brain inflammation, metabolic stress and, consequently, of developing AD at later stages of life. Interrupting deleterious molecular pathways at prodromal stages will likely be the ideal strategy to delay AD progression. The identification of common AD drivers is imperative to establish effective therapeutics, and blocking neuronal metabolic stress at the earliest cognitive symptoms could offer a promising approach to minimize neuronal dysfunction and AD progression. Repurposing labeled anti-diabetic compounds could constitute an interesting option as they have been shown to attenuate AD-linked brain metabolic stress and memory dysfunction (Craft, 2012; De Felice et al., 2014). Future clinical trials may reveal whether these drugs, alone or in combination, are indeed effective in AD.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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