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LIPIDS IN ALZHEIMER'S DISEASE
LES LIPIDES DANS LA MALADIE D'ALZHEIMER

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Topical Issue

Alzheimer's disease as a metabolic disorder

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Abstract – Alzheimer's disease (AD) is defined by memory loss and cognitive impairment, along with the accumulation in brain of two types of abnormal structures, extracellular amyloid plaques and intraneuronal neurofibrillary tangles. Both plaques and tangles are composed predominantly of poorly soluble filaments that respectively assemble from amyloid-β (Aβ) peptides and the neuron-specific, microtubule-associated protein, tau. It is now widely acknowledged that soluble oligomers of Aβ and tau, the building blocks of plaques and tangles, are principal drivers of AD pathogenesis by acting coordinately to impair and destroy synapses, and kill neurons. The behavioral features of AD are a direct consequence of these attacks on synapses and neuronal viability, which in turn reflect a reduced capacity of AD neurons to utilize energy sources needed to maintain neuronal function and vitality. In other words, AD neurons are starving, even when they may be surrounded by abundant nutrients. Here, we review some of the evidence for the metabolic deficiencies of neurons in AD and how they impact neuronal health.

Keywords: amyloid-β / tau / mTOR / insulin / mitochondria

Résumé – La maladie d'Alzheimer en tant que trouble métabolique. La maladie d'Alzheimer (MA) est définie par la perte de mémoire et la déficience cognitive avec l'accumulation dans le cerveau de deux types de structures anormales, des plaques amyloïdes extracellulaires et des enchevêtrements neurofibrillaires intraneuronaux. Les plaques et les enchevêtrements sont composés principalement de filaments peu solubles qui s'assemblent respectivement à partir de peptides amyloïde-β (Aβ) et de la protéine tau spécifique aux neurones, associée aux microtubules. Il est maintenant largement reconnu que les oligomères solubles d'Aβ et de tau, éléments constructifs des plaques et des enchevêtrements neurofibrillaires, sont les principaux moteurs de la pathogenèse de la maladie d'Alzheimer en agissant de manière coordonnée pour altérer et détruire les synapses et tuer les neurones. Les caractéristiques comportementales de la maladie d'Alzheimer sont une conséquence directe de ces attaques sur les synapses et la viabilité neuronale, qui à leur tour reflètent une capacité réduite des neurones, lors de la maladie, à utiliser les sources d'énergie nécessaire pour maintenir la fonction neuronale et la vitalité. En d'autres termes, les neurones de la maladie d'Alzheimer sont affamés, même lorsqu'ils sont entourés de nutriments abondants. Dans cet article, nous passons en revue certaines des preuves des déficiences métaboliques des neurones dans la maladie d'Alzheimer et comment ils affectent la santé neuronale.

Mots clés : amyloïde-β / tau / mTOR / insuline / mitochondries

1 Introduction

The well known behavioral symptoms of Alzheimer's disease (AD) are caused by two phenomena: the compromised function and eventual loss of synapses on neurons that mediate memory and cognition, and by the death of those neurons. A detailed understanding of the molecular mechanisms that cause neuronal decline in AD has been frustratingly slow to develop. Gaining such an understanding, however, is bound to enhance efforts to devise effective means of preventing AD onset or significantly slowing its progression.

While many neurodegenerative disorders are characterized by memory loss and cognitive impairment, AD is distinguished from all others by the accumulation in brain of extracellular

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amyloid plaques and intraneuronal neurofibrillary tangles. The most notable ultrastructural feature of plaques and tangles is tightly packed filaments with diameters in the ~10 nm range and variable lengths. At the biophysical and biochemical levels, both filament types are poorly soluble, but they are composed of distinct building blocks. Whereas the filaments in plaques are made from amyloid-β (Aβ) peptides, which are derived by proteolysis from the widely expressed, single pass transmembrane protein, APP (Kang *et al.*, 1987; Masters *et al.*, 1985), the filaments in tangles assemble from the neuron-specific protein, tau (Grundke-Iqbal *et al.*, 1986; Kondo *et al.*, 1988; Kosik *et al.*, 1988), which is normally found primarily in association with axonal microtubules (Binder *et al.*, 1985; Weingarten *et al.*, 1975).

Because of how visually conspicuous plaques and tangles are in AD brain, it is not surprising that AD research aimed at controlling the disease has been dominated by efforts to block plaques and tangles from forming and eliminate them once they have formed, in the hope that doing so would prevent, reverse or alleviate symptoms. The past 15 years, however, have witnessed a growing realization that the cellular and molecular processes leading to neuronal decline in AD begin decades before symptoms are evident (Villemagne *et al.*, 2013), and that those processes are driven by soluble, misfolded forms of Aβ and tau independently of their respective incorporation into plaques and tangles (Bloom, 2014). Particular progress has been made toward understanding how Aβ oligomers (AβOs) and soluble forms of tau drive synapse loss and neuronal cell cycle re-entry (CCR), the latter of which may lead to the bulk of neuron death in AD (Arendt *et al.*, 2010; Ittner *et al.*, 2010; Seward *et al.*, 2013; Varvel *et al.*, 2008). Emerging from that body of work and related approaches is the realization that AD neurons are chronically undernourished because they cannot effectively use abundant nutrients and trophic factors that surround them.

2 The signaling network for neuronal CCR in AD

Although the degree to which new neurons are produced from neuronal precursor cells in the juvenile and adult mammalian brain has stimulated much debate (Pilz *et al.*, 2018; Sorrells *et al.*, 2018), it is widely agreed that differentiated neurons are permanently post-mitotic. More than 20 years ago, however, evidence for extensive neuronal CCR in AD brain began to accumulate (McShea *et al.*, 1999; Nagy *et al.*, 1997; Yang *et al.*, 2003). Subsequent studies indicated that CCR neurons do not divide, but instead eventually die and may account for the lion's share of neuron death in AD (Arendt *et al.*, 2010). Further observations of high neuronal CCR levels have been made in numerous transgenic mouse models of AD (Li *et al.*, 2011; Norambuena *et al.*, 2017; Seward *et al.*, 2013; Varvel *et al.*, 2008).

The first clues to the mechanism for neuronal CCR followed the observation that oligomers, but neither monomeric nor fibrillar forms of Aβ can drive primary cultured rodent neurons to exit the quiescent G0 state, and express various molecular markers indicative of the G1 and S phases of the cell cycle (Varvel *et al.*, 2008). This AβO-induced neuronal CCR was found to be blocked by inhibitors of mechanistic target of rapamycin (mTOR) signaling, implicating mTOR as a key regulatory factor (Seward *et al.*, 2013; Varvel *et al.*, 2008).

mTOR is a serine-threonine-directed protein kinase present in two multi-protein complexes, mTORC1 and mTORC2. Together, the mTOR complexes respond to extracellular nutrients and trophic factors, such as amino acids, glucose and insulin, to regulate fundamental processes like cell growth, division and survival, and autophagy and mRNA translation, among several others (Zoncu *et al.*, 2011). A principal site of action for mTORC1 is the lysosomal surface, where its activation leads to inhibition of autophagy and promotion of translation (Zoncu *et al.*, 2011).

We recently reported that AβOs and tau work together to cause dysregulation of normal mTORC1 signaling as a requisite step for neuronal CCR (Norambuena *et al.*, 2017). AβOs were found to activate mTORC1 as effectively as amino acids or insulin, but that activation was predominantly at the plasma membrane, at the expense of lysosomal mTORC1. A contributing factor to this mislocalized mTORC1 activation may be AβO-induced, partial loss of mTORC1 from the lysosomal surface. mTORC1-dependent tau phosphorylation at S262 is essential for CCR, and neither selective activation of plasma membrane mTORC1 nor neuronal CCR were observed in AβO-treated tau knockout neurons despite the finding that AβOs simulate mTORC1 in tau knockout neurons as effectively as in wild type neurons. AβOs therefore induce a toxic feedback loop involving tau and mTORC1: tau must be phosphorylated at S262 by mTORC1, or more likely by S6 kinase, which is phosphoactivated by mTORC1, to sustain the mislocalized mTORC1 activation at the plasma membrane that is required for CCR (Norambuena *et al.*, 2017).

Remarkably, the ability of AβOs to induce CCR in cultured neurons can be blocked by insulin, which activates lysosomal mTORC1, or by reducing expression of the lysosome-associated mTORC1 inhibitors, TSC2 or Nprl3 (Norambuena *et al.*, 2017). These observations indicate that while AβO-induced, tau-dependent activation of plasma membrane mTORC1 is necessary for CCR, that effect can be overridden by simultaneous activation of lysosomal mTORC1. They also suggest that boosting insulin signaling in the AD brain might have therapeutic value, and indeed, intranasal insulin delivery is being tested in clinical trials (Claxton *et al.*, 2015; Craft *et al.*, 2017). If intranasal insulin does not prove to be as effective as hoped, it may be because the AD brain has reduced responsiveness to insulin (Steen *et al.*, 2005), a condition initially caused by AβO-induced sequestration of insulin receptors into the neuronal cytoplasm (Bomfim *et al.*, 2012), and later by a dramatic drop in the levels of insulin receptor protein and mRNA (Steen *et al.*, 2005). The well-known reduction of glucose uptake in AD brain is likely a consequence of this reduced insulin signaling and occurs independently of systemic type 2 diabetes, which prompted the idea that AD should be classified as brain-specific, or type 3 diabetes (de la Monte, 2014). Regardless of whether or not type 3 diabetes is a justifiable descriptor of AD, the diminished capacity of the AD brain to respond to insulin and utilize glucose underscores how AD neurons may act as starved cells even when nutrients and trophic factors are in ample supply.

In the context of neuronal CCR, AβOs act as two-edged swords. They are responsible for initiating the insulin

resistance that characterizes AD neurons. This insulin resistance then unleashes the further toxic potential of AβOs to drive post-mitotic neurons back into the cell cycle, which eventually leads to their death.

3 Mitochondrial dysfunction in AD: mTORC1 gone awry again

Mitochondria are the power plants that convert extracellular nutrients into intracellular fuel in the form of ATP. While the reduced ability of AD neurons to utilize extracellular nutrients imposes obvious limits to the activity of their mitochondria, we recently discovered a separate mechanism by which mTORC1 dysregulation by AβOs and tau causes mitochondrial dysfunction (Norambuena *et al.*, 2018). This discovery was based on prior knowledge that the coenzymes, NADH and NADPH, exhibit weak intrinsic fluorescence whose lifetimes increase several-fold when the coenzymes are bound to enzyme partners (Blacker *et al.*, 2014). We first demonstrated that the vast majority of NAD(P)H fluorescence co-localizes with mitochondria, and that ~2/3 of the intrinsic mitochondrial fluorescence in neuronal perikarya is due to NADH, which is involved in glycolysis and the TCA cycle. We then used 2-photon fluorescence lifetime microscopy to measure NAD(P)H fluorescence lifetime as an indicator of mitochondrial activity.

Using that approach, we found that activation of lysosomal mTORC1 by insulin or amino acids stimulates mitochondrial activity. This nutrient-induced mitochondrial activity (NiMA) was found to depend on activation of lysosomal mTORC1, and could be blocked by AβOs in a tau-dependent manner. The ability of AβOs to inhibit NiMA reflects their tau-dependent stimulation of plasma membrane mTORC1 at the expense of lysosomal, mTORC1, which as described earlier is also required for neuronal CCR. Furthermore, mitochondrial DNA replication, as monitored by EdU uptake, was dramatically reduced by insulin or amino acids, but not when AβOs were present. Taken together, these results indicate that lysosomal mTORC1 couples nutrient availability to mitochondrial activity, and links mitochondrial dysfunction to AD by a mechanism dependent on soluble AβOs and tau independently of their integration into plaques and tangles (Norambuena *et al.*, 2018).

4 Conclusions

The AD brain is characterized by reduced insulin sensitivity (Steen *et al.*, 2005) and nutrient (fluorodeoxyglucose) uptake (Mosconi, 2013). A key question that had remained unanswered is whether this reduced metabolic activity of AD brain represents a downstream effect of neuronal deterioration or a prime cause of that deterioration. It now seems clear that impaired metabolic activity lies high upstream in the chain of events that leads to the functional decline and death of neurons in AD. The ability of AβOs to cause acute sequestration into the cytoplasm of insulin receptors (Bomfim *et al.*, 2012) and eventually reduce receptor levels dramatically (Steen *et al.*, 2005) makes it possible for AβOs to drive neuronal CCR, and by extension neuron death (Norambuena *et al.*, 2017). A second, and equally adverse consequence of neuronal exposure to AβOs is inhibition of NiMA. AD neurons are thus surrounded by nutrients and trophic factors that they cannot effectively or efficiently use, and it is therefore no wonder that they spiral into functional and viability decline.

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