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Alzheimer's disease: have we been focusing on the wrong proteins?

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder and the most common form of dementia, characterized by neuronal atrophy in the cerebral cortex and hippocampus[1]. The disease commonly affects those over the age of 65, clinically manifesting as loss of memory and cognitive decline[2]. The neuropathological origins of AD have been classically attributed to misfolded proteins, specifically plaques composed of the amyloid-β (Aβ) peptide and neurofibrillary tangles (NFTs) consisting of aggregates of hyper-phosphorylated tau. Currently no disease-modifying drugs capable of stopping or slowing the progression of the disease exist and only symptomatic treatments are available. As 1 in 85 people worldwide are projected to suffer from AD by 2050, an improved understanding of the disease and the development of novel therapies will become more pressing with each passing year[3].

Amyloid-β and Tau

Aβ is formed from the cleavage of amyloid precursor protein by beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), resulting in peptides of about 40 residues in length[4]. Though most Aβ peptides are harmless Aβ42, an amyloid-β peptide with 42 residues, has the tendency to misfold forming fibrils which can aggregate and develop into plaques[5]. Although the physiological role of Aβ is unclear, the misfolded peptide can induce the formation of β-sheet rich neurotoxic tau oligomers[6]. Tau is a member of the microtubule associated protein class of proteins, and is responsible for stabilizing microtubules and promoting their polymerization in neurons[7]. In AD brains, tau becomes hyper-phosphorylated, self-aggregating into tightly packed filaments and disrupting microtubule structure.

The last 20 years of AD research have focused on developing therapies targeting Aβ with little success. Particularly the failure of Aβ antibodies, capable of reducing plaque density in the brain, as well as Aβ vaccinations in improving cognition or functional ability, coupled with the existence of cognitively healthy individuals with abnormally high levels of Aβ has called into question the soundness of the "amyloid hypothesis"[8-11]. Focus is slowly shifting to tau as the target of choice in treating AD, although two recent trials aimed at reducing tau hyper-phosphorylation ended in failure[12,13]. However, a growing body of evidence is suggesting that the scientific community has been focusing on the wrong proteins and that improved understanding of insulin, rather than Aβ or tau, may hold the key to treating AD.

Link between Alzheimer's disease and Insulin Resistance

The human insulin protein is comprised of 51 amino acids and is secreted from pancreatic β cells into the blood stream in response to high levels of plasma glucose[14]. Through binding with the insulin receptor, insulin can promote cellular uptake of glucose from the blood. Insulin resistance is a hallmark of type 2 diabetes (T2D) and occurs when cells are unresponsive to insulin and fail to absorb glucose. Chronic insulin resistance can lead to renal and cardiovascular disease as well as blindness[15,16]. Interestingly, in AD, insulin resistance is also observed in the body and brain, with patients commonly possessing high fasting plasma glucose levels, hyperinsulinemia, and impaired glucose tolerance[17]. Indeed, a quick glance at an FDG- PET scan reveals glucose metabolism is reduced throughout much of the brain in those with AD[18].

There is a great deal of epidemiological evidence linking AD and the insulin resistance commonly observed in diabetes. In the Rotterdam cohort study, where over 6000 individuals were followed for as many as 6 years, diabetes was found to double the risk of developing dementia[19]. Recent work by Xu et al. confirmed these findings and, in their sample, risk of developing AD or vascular dementia increased three times in those with diabetes[20]. As insulin stimulates glucose absorption in the brain, it is possible that insulin resistance may lead to neuronal energy imbalance and oxidative stress, causing the accumulation of misfolded proteins commonly implicated in AD pathogenesis. Supporting this claim, mouse studies have shown disruption of pancreatic insulin secretion or neuronal insulin receptor expression can lead to formation of plaques and tangles as well as cognitive decline[21,22].

Viewing Alzheimer's disease through the lens of Insulin Resistance

Elucidating the link between AD and insulin resistance may help shed light on the processes that culminate in the formation of plaques and tangles. One of the causes of amyloid plaque accumulation may be an imbalance in the clearance and production of Aβ. Interestingly, a recent study on rats demonstrated that chemically stimulated insulin deficiency leads to increased expression of BACE1, the enzyme involved in the breakdown of amyloid precursor protein to Aβ[23]. This, coupled with the fact that insulin can suppress expression of amyloid precursor protein, suggests how insulin resistance

could push the equilibrium in favour of Aβ production24. Insulin also promotes release of Aβ from in vitro cell cultures and accelerates trafficking of the protein from the Golgi apparatus to the plasma membrane25. Hence, insulin resistance may lead to more Aβ remaining within the cell where it can potentially form into plaques.

Insulin resistance may also serve to explain the underlying tau pathology of AD. One of the mechanisms by which tau hyper-phosphorylation can occur is through over-activity of its many kinases. One main tau kinase is glycogen synthase kinase 3 (GSK3) and overexpression of GSK3 in mouse brains was found to induce hyper-phosphorylation of tau[26]. Normally, the binding of insulin to its receptor leads to the recruitment of phosphatidylinositol 3-kinase (PI3K) which activates a number of downstream effectors ultimately leading to GSK3's phosphorylation[27]. As phosphorylation of GSK3 induces a conformational change that masks the protein's active site, in this way insulin can inhibit GSK3 activity[28]. Insulin resistance will therefore lead to increased levels of GSK3 activity, stimulating hyper-phosphorylation of tau and partially explaining the NFTs commonly observed in AD.

Insulin-Related AD Therapies

Several clinical trials and cohort studies have shown therapies targeting the insulin resistance component of AD can have significant efficacy. One early trial with twenty five participants found daily intranasal insulin treatment allowed greater retention of verbal information and improved attention in patients with early AD[29]. A larger, more recent trial with 104 individuals found AD participants given intranasal insulin experienced improvements in memory and functional ability[30]. Importantly, no adverse events were reported for the insulin therapy and larger and longer studies investigating insulin as a therapeutic for AD must be conducted.

Apart from insulin, another potential therapy for AD is metformin, the most commonly used drug to treat insulin resistance in diabetes. Unfortunately, few if any randomized control trials investigating metformin's impact on AD have been conducted and observational studies must be used to gauge metformin's potentially beneficial effects. In a large cohort study of approximately 150000 individuals with T2D from Taiwan, taking metformin was found to reduce risk of dementia by approximately 35% in 8 years[31]. In contrast to these findings, a large case-control study from the United Kingdom found that individuals were at slightly higher risk of developing AD if they received metformin in the long-term[32]. Clearly, more research must be done to investigate metformin's clinically efficacy in treating AD.

Conclusion

A growing body of evidence is suggesting we begin to view AD, not as a protein misfolding disorder, but rather as a metabolic one. If AD truly does stem from insulin resistance, and it is insulin resistance that ultimately stimulates the formation of misfolded amyloid and tau, the failure of therapies targeting these proteins could be easily explained as the chief cause of AD is not being addressed. Interestingly, of the few drugs actually approved to treat AD, none of them even interact with amyloid-β so it is curious that the scientific community continues to pursue amyloid-β centered therapies with such constricted vision. Clearly a new approach to combating AD is required and a deeper understanding of insulin's role in protein misfolding pathways will help guide future efforts to slow and reverse the progression of AD. Hopefully in the coming years the relationship between insulin resistance and AD will be more readily recognized by clinicians and researchers and pursued with as much fervour as the amyloid hypothesis.

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