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Targeting diminished cerebral glucose metabolism for Alzheimer's disease

As demographics of developed countries shift toward an older population, the number of cases of Alzheimer's disease is anticipated to increase dramatically. Currently, there are no disease modifying treatments and approved drugs provide only symptomatic relief. Amyloid beta has been the primary drug target over the last several years, yet has not yielded any new drug approvals. Another feature of Alzheimer's disease, diminished cerebral glucose metabolism, may offer new targets for drug development.

By Dr Henderson

Alzheimer's disease (AD) is a devastating age-associated neurodegenerative disease characterised by a progressive decline in cognitive abilities. Clinical signs of AD include memory loss that disrupts daily life, difficulty in completing daily tasks and difficulties with language. Each of these symptoms progress until the patient becomes incapacitated. The prevailing theory to explain the pathophysiology of AD is the amyloid cascade hypothesis. This hypothesis is based on both the neuropathology and genetic links to early onset forms of the disease. The neuropathology of AD is characterised by the deposition of fibrillar amyloid-β (Aβ) peptides, amyloid plaques (AP) and accumulation of neurofibrillary tangles (NFT), mainly composed of tau protein. The prevalence of Aβ species in the brains of patients with AD has led support to the amyloid cascade hypothesis as the fundamental causative

mechanism in the pathogenesis of AD. This hypothesis has been further reinforced by the association between early onset AD and rare mutations in the genes *APP* (Amyloid Precursor Protein), *PSEN1* (Presenilin-1) and *PSEN2* (Presenilin-2). Mutations in these genes lead to early-onset (<60 years) familial AD, which represents about 5% of AD cases. A prolific research effort has demonstrated that these mutations result in altered processing of the APP protein and generation of toxic forms of Aβ. With this combination of genetics and pathology, the amyloid hypothesis has remained the dominant theory in the field and has attracted the lion's share of drug development[1].

Unfortunately, the amyloid cascade hypothesis has yet to yield any treatments for AD. Drugs candidates have targeted various aspects of Aβ generation and clearance, ranging from gamma secretase inhibitors designed to limit the production of toxic

AD < Controls

MRI
FDG-PET
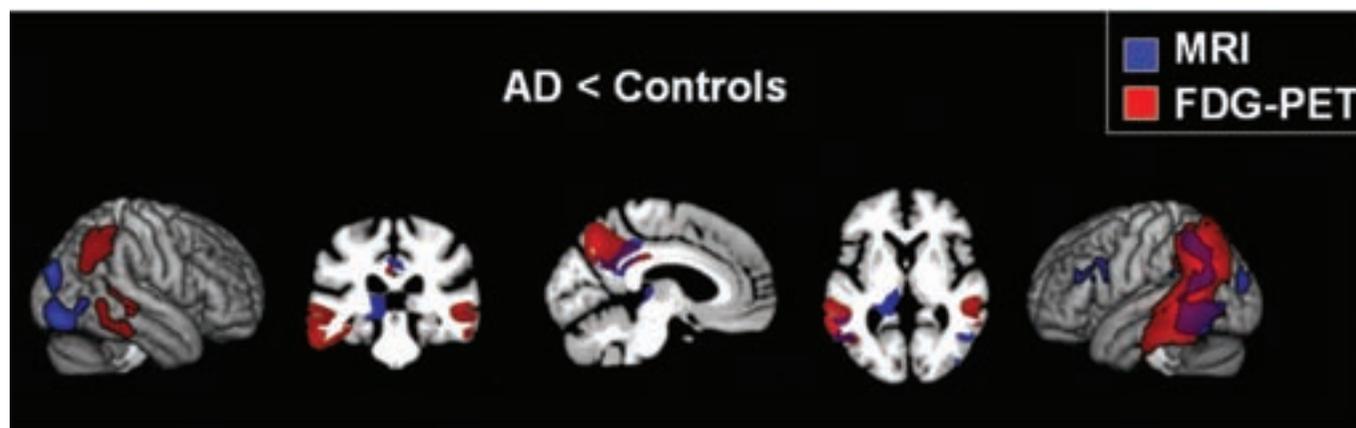
forms of Aβ and more recently, immunotherapy approaches designed to specifically remove Aβ from the brain. These studies have uniformly failed to achieve primary endpoints in Phase III trials. While the amyloid cascade hypothesis has solid footing in both genetics and pathology of the disease, and considerable resources are still being devoted to it, it may be time to seriously consider other aspects of AD pathology that may offer another angle to tackle this difficult disease.

One such aspect is diminished cerebral glucose metabolism (DCGM). DCGM is a prominent, well-characterised feature of AD[2]. Starting in the 1980s, studies examining brain glucose metabolism in patients with AD by FDG-PET found DCGM in patients with probable AD compared to normal controls (**Figure 1**). In these studies, significant correlations were found between DCGM and worsening performance on measures of cognitive function. The DCGM found in AD is not a general decrease in glucose utilisation but instead is associated with specific regions of the brain. Most notably, DCGM is found in the posterior cingulate and parietal, temporal and prefrontal cortices. This pattern of DCGM has been identified in at-risk individuals well before clinical signs of dementia become evident, and even in young adults. Interestingly, the regions afflicted with DCGM are associated with the brain's default network, which is a series of connected regions of the brain that are most active when one is resting quietly with closed eyes. The default network is thought to function in spontaneous cognition; thoughts that do not require outside stimuli. These activities include planning for the future, daydreaming and importantly, memory retrieval. Various studies have mapped the default network to an interconnected network comprising the prefrontal cortex, posterior cingulate,

parietal lobule and temporal cortex. Several studies have suggested that the default network may be predisposed to develop AD pathology due to the high rates of glucose metabolism found compared to other brain regions[3].

The characteristic pattern of DCGM is an early event in AD and has been noted in both mild cognitive impairment (MCI) and pre-clinical AD. Mild cognitive impairment is characterised by subjective complaints of memory problems, which are not serious enough to interfere with daily living and is considered a risk state for later development of dementia. As many as 50% of MCI patients will progress to dementia, particularly AD. The potential relationship between DCGM to AD can be demonstrated in longitudinal studies which demonstrate the progressive worsening of DCGM as individuals progress from pre-symptomatic AD to MCI and ultimately to AD.

Despite the early occurrence of DCGM, the precise cause remains elusive. Historically, the DCGM seen in AD has been viewed as representing loss of synaptic activity either through cell atrophy or reduction in synaptic and dendritic fields. However, increasing evidence has pointed to a fundamental cellular or metabolic defect in AD, and perhaps a primary role of DCGM in the etiology of the disease. Several recent studies in transgenic mouse models of AD, suggest that metabolic disturbances occur before the widespread generation or deposition of Aβ and may be related to deficits in cellular trafficking of mitochondria. These findings are consistent with the roles of *APP* and *PSEN* in intracellular trafficking. The *APP* and *PSEN* protein complexes are thought to play a role in facilitating the movement of lipid rich cargos up and down axons. Disruption of this trafficking within the narrow confines of an axon has been proposed to result in 'neuronal traffic jams' that

Figure 1
Diminished Cerebral Glucose Metabolism (DCGM) in Alzheimer's disease. Differences between Alzheimer's disease patients and age-matched controls in brain glucose utilisation (FDG-PET, red) and atrophy (MRI, blue). Areas of overlap are shown in violet. Adapted from Frisch et al 2013[2]

Despite the brain's reliance on glucose for energy, little glycogen is stored in the brain, and instead the brain relies on circulating glucose for much of its function. The reliance on circulating glucose and lack of use of fat, makes the brain especially vulnerable to dysfunction of either glucose transport or utilisation. This is well illustrated in cases of *GLUT1* deficiency syndrome. Glucose is transported into the brain by the *GLUT1* and *GLUT3* transporters. The *GLUT1* protein is prominently expressed in the cerebral microvasculature and transports the majority of glucose into the brain. Due to the substantial glucose requirements of the brain, both copies of the *GLUT1* gene must be present to properly supply the brain. In cases where one copy of the gene is non-functional, insufficient glucose is provided to the brain and clinical features of the disease are evident and severe including seizures, hypotonia, ataxia, language deficits and microcephaly.

Therapeutic strategies

The early occurrence of DCGM in MCI and AD makes it an attractive target for intervention and several different strategies have been investigated. One promising area is the induction of ketosis.

In the case of *GLUT1* deficiency syndrome, one avenue of intervention is the induction of ketosis by adherence to a ketogenic diet. The rationale for induction of ketosis is to provide the cells that are having difficulty using glucose with another substrate they can metabolise. Although the brain is fairly limited in its fuel use, it can use glucose and ketone bodies. Ketone bodies are comprised of three compounds; beta-hydroxybutyrate, acetoacetate and acetone. Ketone bodies are normally produced by the liver from fatty acids under conditions of low glucose availability, such as during extended fasting or when carbohydrates are restricted from the diet. The elevation of ketone bodies in circulation is called ketosis. One function of ketosis is to provide an alternative to glucose for the brain during periods of food deprivation or low glucose availability. The use of ketone bodies by the brain has been demonstrated in classic experiments performed in the 1960s which demonstrated that under extended fasting, the concentration of the ketone bodies in the blood is greatly elevated and can provide up to 60% of the brain's energy needs. Therefore, the induction of ketosis can provide a supplemental energy source to the brain under conditions where glucose is low, for example in *GLUT1* deficiency syndrome. A similar rationale may be applied to the DCGM found in AD.

may inhibit vital cellular functions such as mitochondrial plasticity[4].

Yet, since the vast majority of patients who develop AD do not have mutations in *APP* or *PSEN1/2* and they still develop early DCGM, this observation raises the possibility that the early metabolic disturbances are causing altered processing of *APP*. Interestingly, this has been shown in several model systems. Chronic energy depletion in mouse models of AD generate increased levels of A and amyloid load. These studies suggest that chronic, low-level, energy stress, such as that seen in DCGM, may alter the activities of *APP* processing enzymes ultimately leading to the pathology of AD. Therefore, the early DCGM may be leading to conditions that mimic mutations in *APP* and *PSEN1/2*. Combined, this makes DCGM an attractive target for intervention (**Figure 2**).

Brain energy metabolism

Deficits in glucose metabolism, such as DCGM, present a real challenge for the brain. The brain is one of the most metabolically active organs in the body. Yet, unlike many other organs in the body, it does not efficiently metabolise fat as an energy source. Measurements of ateriovenous differences across the brain reveal very little extraction of fats, but large extraction of glucose and oxygen. Under most normal conditions, the brain relies almost exclusively on substantial amounts of glucose for its energy needs. While the brain is only about 2% of body weight, it accounts for about 25% of total body glucose use and about 20% of total oxygen use. The majority of the extracted glucose is oxidised to generate energy.

Ketogenic diets

Ketogenic diets (KDs) became of interest in the 1920s when they were developed to reduce the occurrence of seizures in epileptics. The rationale for this type of diet was based on the ancient observation that fasting reduced seizures. In the 5th century, Hippocrates noted that a man suffering from epilepsy was cured by abstaining from all food and drink. In the King James Version of the Bible, a story describes how Jesus cured an epileptic boy (**Figure 3**). When asked how he did it, Jesus responded that, "this kind can come out by nothing but prayer and fasting". KDs were developed to mimic the physiological changes seen in extended fasting. KDs are very low in carbohydrates and proteins and very high in fat and have been used successfully for many years to treat refractory childhood epilepsy.

Ketogenic diets have been employed in several neurological disorders including mild cognitive impairment. In 2010, Krikorian and co-authors reported the results of a study of 23 older adults with memory complaints placed on a KD for six weeks. After six weeks on the KD memory performance improved and the improvement correlated with the patient's level of ketosis[5]. Unfortunately, the strict limitation on carbohydrate intake makes adherence to a KD challenging. This is particularly true for patients with AD who have documented shifts in food preference toward sweet foods, making compliance to a KD difficult.

Ketogenic agents

An alternative to a KD is to induce ketosis without change in diet. One way this has been done is with special fats called medium chain triglycerides (MCTs). MCTs are triglycerides comprised of fatty acid chains between 5-12 carbons. Fatty acids normally encountered in the diet are long chain fatty acids (LCT) with chains between 18-22 carbons. Due to the short chain lengths of medium chain fatty acids, MCTs are not subject to the regulation imposed on long chain fatty acids and are well known for their ketogenic properties. Importantly, the oxidation of medium chain fatty acids occurs regardless of carbohydrate in the diet and can induce ketosis without modification of the diet.

Two studies have been reported using MCTs to induce ketosis in mild to moderate AD patients. The first study was a single dose, crossover design. The second was a 90-day study with once-a-day dosing. Each of these studies demonstrated improvement in cognition in a predefined genetic sub population of the participants[6]. Such studies are encouraging and offer the possibility that the induction of ketosis may prove a relatively low risk intervention in mild to moderate AD. Larger more comprehensive studies are currently under way with this approach.

Insulin signalling

Another target is the insulin and insulin-like growth factor signalling pathways. As discussed above, several lines of evidence suggest that AD is fundamentally a metabolic disease in which brain glucose utilisation and energy production are impaired. Several lines of evidence suggest that the metabolic disturbance is due to disruption in brain insulin and insulin-like growth factor (IGF) signalling pathways. Such pathways regulate neuronal survival and energy production. The development of resistance in these pathways, either through dietary factors or activities of Aβ, could lead to progressive disruption in energy generation and cell survival. This hypothesis is sometimes referred to as type 3 diabetes or 'Brain Diabetes'[7].

Studies done targeting insulin and insulin-like signalling have met with some success. Notable among these interventions is the application of nasal insulin. As with diabetes, the resistance to insulin can be overcome by provision of more insulin. Systemic provision of insulin would have profound effects on circulating glucose; therefore, to avoid possible harmful side-effects, insulin has been administered intranasal to target the brain directly. Published studies have found that such treatments increase brain insulin levels and improve performance memory tasks while having little effect on plasma glucose and insulin levels.

Figure 3
Jesus cures an epileptic boy. Engraving by Otto Elliger depicts Jesus healing an epileptic boy by casting out a demon, after his disciples were unable to do so. *Courtesy of the Digital Image Archive, Pitts Theology Library, Candler School of Theology, Emory University*

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Larger, more comprehensive studies are currently under way with this approach[8].

Conclusions

With only the currently available treatments, the prevalence of AD is predicted to increase dramatically in the next 40 years. Current treatments, while effective, do not significantly slow the progression of the disease, and new therapies are desperately needed. A tremendous research effort over the last 10 years has greatly increased our understanding of AD. Many exciting therapies have been developed over the years, but have not produced the results we would all like to see in the clinic.

Addressing another aspect of AD pathology, such as DCGM, is a relatively new area of research yet offers the promise of many different avenues of attack. Addressing low glucose availability by the induction of ketosis is one such promising approach. Addressing the insulin/IGF signalling pathway is another. Fortunately, both of these approaches have entered larger clinical trials and results are expected within a few years.   **DDW**

Trained in Genetics, Dr Henderson is now Vice President of Research and Development at Accera, a biotechnology company focused on cognition and the use of ketone bodies in neurodegenerative diseases. He received his B.A. in Biology from Washington University, St. Louis, MO and his Ph.D. in Molecular Genetics and Cell Biology from University of Chicago. He received extensive post-doctoral training in developmental biology at the University of Wisconsin. Dr. Henderson is the scientific founder of Accera.