

# Diminished cerebral glucose metabolism: A key pathology in Alzheimer's disease

More than three decades of research have revealed that diminished cerebral glucose metabolism (DCGM), also known as glucose hypometabolism, is a key underlying pathological change in the Alzheimer's brain.<sup>1</sup> DCGM leaves a large portion of the brain's energy needs unfulfilled and may contribute to cell death and cognitive dysfunction.<sup>2</sup> Given that DCGM occurs years before other well-known hallmarks of the disease have been detected, it is unlikely to be the result of cell loss and may precipitate other downstream pathological events.<sup>2</sup> Targeting DCGM represents a promising new therapeutic strategy for patients with Alzheimer's disease (AD).

## Declines in cerebral glucose metabolism impair cognitive function

The human brain is one of the most metabolically active organs in the body and metabolizes a large amount of glucose to produce adenosine triphosphate (ATP).<sup>1</sup> Despite its high energy demands, the brain is relatively inflexible in its ability to utilize substrates for energy production and relies almost entirely on circulating glucose for its energy needs.<sup>1,2</sup> This dependence on glucose puts the brain at risk if the supply of glucose is interrupted, or if its ability to metabolize glucose becomes defective.<sup>2</sup> If the brain is not able to produce ATP, synapses cannot be maintained and cells cannot function, ultimately leading to impaired cognition.<sup>2</sup>

## DCGM is a well-characterized feature of AD

DCGM was an early observation in AD. Studies from almost 30 years ago found a 17%-24% decline in cerebral glucose metabolism in patients with AD, compared with age-matched controls.<sup>3</sup> Numerous imaging studies have since confirmed this observation.<sup>1</sup>

Abnormally low rates of cerebral glucose metabolism are found in a characteristic pattern in the AD brain, particularly in the posterior cingulate, parietal, temporal, and prefrontal cortices. This pattern is reproducible and has even been proposed as a diagnostic tool for AD. Interestingly, regions of the brain showing DCGM overlap with regions identified in the default network.<sup>1</sup>

## It is unlikely that DCGM is a result of cerebral atrophy

In a pivotal study, Reiman and colleagues demonstrated how early the pathology can begin. The study compared cerebral glucose metabolism in patients with probable AD and young adults (mean age 30.7 years) at high genetic risk of AD (APOE4 carriers). The young adult APOE4 carriers showed no signs of cognitive impairment or plaque deposition, yet DCGM was detected in the same areas of the brain as subjects with AD.<sup>4</sup>

DCGM is not exclusive to APOE4 carriers. By the time Alzheimer's has been diagnosed, DCGM occurs consistently across genotypes APOE3/E4, APOE3/E3, and APOE4/E4.<sup>5</sup>

Given that DCGM occurs before other clinical and pathological changes occur, it is unlikely to be due to the gross cell loss observed in AD.<sup>2</sup>

## Targeting DCGM in AD

Improving memory performance by chronically raising glucose levels has had some success in animal models and humans. However, this approach is impractical and may not address the problem of DCGM, particularly as glucose levels generally remain normal in AD. This has led to the exploration of alternative fuel sources, such as ketones, to help fuel the brain.<sup>2</sup>

## Fueling the brain with ketones in neurodegenerative diseases

During times of diminished cerebral glucose metabolism, the brain is able to use ketones as a back-up fuel source. When glucose levels are low, for example when food is scarce, the liver is naturally triggered to generate ketones as a survival mechanism.<sup>1</sup>

In AD, this natural ketone back-up system can be harnessed to address DCGM. Preclinical and clinical research has shown that exogenously raising ketone levels is neuroprotective and can improve memory and cognition.<sup>6-8</sup> Indeed, ketogenic diets have a long and successful clinical history. However, they can be impractical, particularly in patients with AD.<sup>2</sup>

## Safe elevation of ketone levels

Inducing ketosis through the administration of medium-chain triglycerides (MCTs) has produced promising results in AD. MCTs have unique ketogenic properties due to their short fatty acid chain lengths. Importantly, MCTs are converted to ketones regardless of other macronutrients consumed; therefore, no dietary restrictions are required.<sup>1</sup>

Now, there is a prescription **medical food** available that safely increases the concentration of ketones. Axona<sup>®</sup> contains MCTs that are converted to ketones in the liver and then transported to the brain to be used as fuel instead of glucose.<sup>9</sup>

## Fuel memory and cognition by targeting DCGM in AD

In a clinical trial, Axona enhanced memory and cognition in patients with mild to moderate AD. Approximately 80% of trial patients took Axona in combination with one or more approved medications for AD. At the end of the trial period, patients continued with their existing medication, but stopped taking Axona. During this time, the significant effects of Axona ceased and obvious declines were noted.<sup>10</sup>



Axona is the only available therapy that addresses diminished cerebral glucose metabolism, an underlying pathology of AD. Current treatments only target symptoms of the disease.<sup>1</sup> Adding Axona to traditional treatments addresses different aspects of AD at the same time and can help make the biggest impact in enhancing memory and cognition.<sup>10</sup>

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