



ABSTRACT

Ketone and brain energy metabolism during aging: implications for treating Alzheimer's disease.

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A chronic brain energy deficit is an important pre-symptomatic feature of Alzheimer's disease (AD) that requires closer attention in the development of AD therapeutics. Our rationale is fourfold: (i) Brain uptake of its main fuel, glucose, is already lower in the frontal cortex of people >65 years old despite cognitive scores that are normal for age. (ii) The regional deficit in brain glucose uptake is present in adults <40 years old who have genetic or lifestyle risk factors for AD but in whom cognitive decline has not yet started. Examples include young adult carriers of presenilin-1 or apolipoprotein E4, and young adults with mild insulin resistance or with a maternal family history of AD. (iii) Brain glucose uptake is impaired in AD and mild cognitive impairment (MCI) but, importantly, brain uptake of ketones (beta-hydroxybutyrate and acetoacetate), the main alternative fuels to glucose, remains the same in AD and MCI as in cognitively healthy age-matched controls. (iv) Recent clinical trials show that a ketogenic diet or a ketogenic supplement raises ketone availability to the brain and improves cognitive outcomes in both MCI and AD as well as in acute experimental hypoglycemia. These observations demonstrate that the brain fuel deficit in older people is specific to glucose, precedes cognitive decline associated with AD, and becomes more severe as MCI progresses towards AD. Clearly, gradual brain energy exhaustion caused is contributing significantly to the onset and/or progression of AD. However, since both the capacity of the brain to take up ketones is still normal in MCI and in early AD and because cognitive improvement can be achieved with ketogenic interventions, it seems that brain dysfunction in AD is because the brain is starved of energy (glucose, specifically) and not because of brain cell death as generally assumed. We suggest that the brain energy (glucose) deficit needs to be overcome in order to successfully develop more effective therapeutics for AD (and other neurodegenerative diseases). At present, oral ketogenic supplements are the most promising means of achieving this goal.