Deteriorating brain glucose uptake increases the risk of Alzheimer's disease: Could medium chain triglycerides be of therapeutic benefit?

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Brain glucose uptake is well-known to be deteriorating in Alzheimer's disease (AD) in brain regions with the most neuropathology[1]. We developed the ketone PET tracer, ^{11}C-acetoacetate, and have reported that in contrast to 17-33% lower glucose uptake in certain brain regions, brain ^{11}C-acetoacetate uptake is still normal in mild AD compared to cognitively normal, age-matched older persons[2,3]. Hence, brain energy failure in mild AD appears to be limited to glucose. We observe a similar pattern of brain glucose uptake deficit in young adults with insulin resistance as in mild AD. Normal human brain function can still be maintained when up to ~2/3 of brain fuel requirements are met by ketones (β-hydroxybutyrate and acetoacetate) instead of glucose, i.e. during prolonged fasting or strenuous exercise[1].The implications are that - (i) memory loss in mild AD could potentially still be corrected or bypassed using ketones which are the body's physiological alternative brain fuel to glucose because brain ketone uptake is still intact in mild AD, and (ii) deteriorating brain glucose uptake with age may depend as much on insulin resistance as on aging per se. Medium chain triglycerides (MCT) have cognitive benefits when brain glucose uptake is compromised, i.e. GLUT (glucose transporter) deficiency[4],type 1 diabetes[5], or mild-moderate AD[5,6]. Certain MCT not only raise brain ketone uptake but may improve brain energy metabolism in humans[4]. Our view is that optimal brain fuel metabolism is crucial for healthy cognition in older persons. We suggest that medications for AD, regardless of their target, will not have a chance to be fully effective unless the glucose deficit in the AD brain is bypassed or reversed early enough to allow exhausted neurons to receive sufficient fuel so as to respond to the drug and function more effectively. The potential of keto-therapeutics to maintain cognition warrants further study especially in older persons.

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Supported by CIHR, CFI, CRC, CFQCU, FRQS, USherbrooke Research Chair.