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Can ketones compensate for deteriorating brain glucose uptake during aging? Implications for the risk and treatment of Alzheimer's disease

Stephen C. Cunnane,[1,2,3] Alexandre Courchesne-Loyer,[1,3] Valérie St-Pierre,[1,3] Camille Vandenberghe,[1,3] Tyler Pierotti,[1,4] Mélanie Fortier,[1] Etienne Croteau,[1] and Christian-Alexandre Castellano[1]

[1]Research Center on Aging, and [2]Departments of Medicine and [3]Pharmacology and Physiology, Université de Sherbrooke, Sherbrooke, Québec, Canada. [4]Department of Biology, Bishop's University, Sherbrooke, Québec, Canada

Address for correspondence: Stephen C. Cunnane, Research Center on Aging, 1036 Belvedere St. South, Sherbrooke, Québec, Canada J1H 4C4. stephen.cunnane@usherbrooke.ca

Brain glucose uptake is impaired in Alzheimer's disease (AD). A key question is whether cognitive decline can be delayed if this brain energy defect is at least partly corrected or bypassed early in the disease. The principal ketones (also called ketone bodies), β-hydroxybutyrate and acetoacetate, are the brain's main physiological alternative fuel to glucose. Three studies in mild-to-moderate AD have shown that, unlike with glucose, brain ketone uptake is not different from that in healthy age-matched controls. Published clinical trials demonstrate that increasing ketone availability to the brain via moderate nutritional ketosis has a modest beneficial effect on cognitive outcomes in mild-to-moderate AD and in mild cognitive impairment. Nutritional ketosis can be safely achieved by a high-fat ketogenic diet, by supplements providing 20–70 g/day of medium-chain triglycerides containing the eight- and ten-carbon fatty acids octanoate and decanoate, or by ketone esters. Given the acute dependence of the brain on its energy supply, it seems reasonable that the development of therapeutic strategies aimed at AD mandates consideration of how the underlying problem of deteriorating brain fuel supply can be corrected or delayed.

Keywords: Alzheimer's disease; glucose; ketones; beta-hydroxybutyrate (β-HB); acetoacetate (AcAc); medium-chain triglycerides (MCT)

Introduction

The adult brain requires a disproportionately large energy supply; while it represents about 2% of body weight, it consumes about 20–23% of whole-body energy requirements, mostly in the form of glucose. It is now well established that both uptake and metabolism of glucose by the brain deteriorate in Alzheimer's disease (AD). There is a particular pattern of regional brain glucose hypometabolism in AD affecting the parietal and temporal cortices, where the glucose deficit is on the order of 20–25% compared to age-matched, cognitively normal controls.[1] Because of a loss of synapses and neuronal dysfunction and death in AD,[2] the deficit in brain glucose utilization has generally been interpreted to be a consequence of AD (e.g., fewer functioning neurons decreases the need for glucose). This perspective is indeed logical but does not account for multiple examples of conditions in which regional brain glucose hypometabolism is present in presymptomatic individuals at risk of AD (i.e., before the clinical (cognitive) onset of the disease). There are several clear examples in which enhanced genetic or lifestyle-based risk of AD causes lower brain glucose uptake long before the onset of cognitive symptoms.

Glucose is the brain's predominant fuel but, like other organs, the brain has a back-up fuel for occasions when glucose supply is insufficient, for example, during fasting, starvation, strenuous exercise, or malnutrition. Unlike other organs for which free fatty acids replace insufficient availability of glucose, the brain uses ketones

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Table 1. Presymptomatic brain glucose hypometabolism in persons at risk of Alzheimer's disease (AD)

Group at risk	Age (years)	Brain region with lower brain glucose uptake	Magnitude of brain glucose deficit (% lower than control (100%))	Reference
Carriers of presenilin 1	30	Posterior cingulate; parietal and temporal cortices	~20	Schöll *et al.*[6]
Carriers of apolipoprotein E4	31	Prefrontal, parietal, temporal cortices; posterior cingulate	~10	Reiman *et al.*[11]
Maternal family history of AD	43	Parietal cortex, temporal cortex, hippocampus, entorhinal cortex, posterior cingulate	~15	Mosconi *et al.*[10]
Cognitively normal, prediabetic older persons	74	Prefrontal, temporal, parietal cortices; posterior cingulate; precuneus	Lower (actual magnitude not provided)	Baker *et al.*[29]
Young women with polycystic ovary syndrome	25	Frontal cortex, middle temporal cortex	~12	Castellano *et al.*[13]
Cognitively normal older persons	72	Frontal cortex	~12–15	Nugent *et al.*[17]

(also known as ketone bodies) as the only significant back-up fuel for glucose. The two ketones that replace glucose for the brain are β-hydroxybutyrate (β-HB) and acetoacetate (AcAc). They are normally present in plasma in a ratio of 2:1–3:1 in favor of β-HB, but it is only AcAc that is β-oxidized in mitochondria; therefore, β-HB must be converted to AcAc before being metabolized. The third ketone, acetone, is a volatile decarboxylation product of AcAc, the excretion of which on the breath correlates well with plasma ketone levels.[3]

We discuss here how brain glucose hypometabolism could not only be a consequence of AD but could also be contributing to the risk of AD presymptomatically. We also compare findings on the problem of deteriorating brain glucose uptake to recent findings on brain ketone uptake in cognitively healthy older people and in AD, and make reference to the emerging literature on the therapeutic potential of ketogenic supplements or diets in AD. This review complements recently published reviews on changing brain energy metabolism.[4,5] Moreover, it extends the discussions in these reviews by providing more information about the differences between brain glucose and ketone uptake in AD, as well as proposing a therapeutic objective for the dose of ketogenic treatments that could be expected to have therapeutic benefit in AD.

Presymptomatic brain glucose hypometabolism contributing to the onset of AD

Carriers of the presenilin 1 mutation are at the highest risk of AD.[6–8] Carriers of the apolipoprotein E4 allele and persons with a family history of AD, especially on the maternal side, are also at increased risk of AD,[9–12] although their risk is still relatively low compared to presenilin 1 carriers. Type 2 diabetes and its associated insulin resistance rank among the most important of the nongenetic or predominantly lifestyle-based risk factors for AD. In these three situations, presymptomatic regional brain glucose hypometabolism on the order of 15% is clearly present despite results on cognitive batteries being normal (Table 1). Glucose hypometabolism in those at risk of diabetes is most frequently, but not exclusively, observed in the frontal cortex and, in certain cases, can be observed at ages as young as 24 years.[13]

We interpret these data (Table 1) to indicate that presymptomatic brain glucose hypometabolism can be present long before the threshold of cognitive symptoms of AD and could therefore potentially

be contributing to the development and/or progression of the cognitive decline associated with AD. A neuropathological link has not yet been convincingly demonstrated in humans, but it is clearly the case in amyloid precursor protein (APP) transgenic mouse models of AD, in which various experimental approaches to diminishing brain glucose supply all drive amyloid beta overproduction.[14] Nevertheless, the pattern of regional brain glucose hypometabolism varies across these different conditions; therefore, it remains speculative as to how they could contribute to AD. We also note that although mild cognitive impairment (MCI) is now widely recognized as a prodromal state to AD and displays regional brain glucose hypometabolism, objective evidence for cognitive deficits is already present in MCI; we have therefore excluded it from Table 1 as an example of a presymptomatic condition to AD.

Aging is also a significant risk factor for AD. We and other researchers have used positron emission tomography (PET) with the glucose analogue and radiotracer ^{18}F-fluorodeoxyglucose (FDG) to study brain energy metabolism in cognitively normal older persons. Using quantitative PET-FDG, we have shown that in cognitively normal people averaging 72 years, the cerebral metabolic rate of glucose (CMRg) in the superior frontal cortex is approximately 35 $\pm$ 5 instead of the 40 $\pm$ 7 mmol/100 g/min as seen in young adults (i.e., the glucose uptake deficit in this brain region is on the order of 12–15%).[15–17] CMRg did not differ significantly between young and older adults in either white or gray matter as a whole, nor did it differ in the temporal or parietal cortices where CMRg noticeably decreases in AD. Lower CMRg present mostly, if not exclusively, in the frontal cortex of cognitively normal older people has been previously reported.[1,18] Thus, lower CMRg in the temporal and parietal cortices in AD is a fundamentally different situation than lower CMRg in the frontal cortex during cognitively normal aging (but the former may arise from or be related to the latter). Widespread cortical thinning and regional brain atrophy are also present in older people with normal cognition;[17] therefore, although lower frontal CMRg can clearly be presymptomatic in relation to aging-associated cognitive decline, it is by no means the only or even the quantitatively most significant change occurring in the brain during aging.

These observations suggest that the widespread perception that brain glucose hypometabolism is uniquely a consequence of synaptic dysfunction and neuronal failure or death associated with aging needs to be reevaluated. Indeed, this regional brain glucose hypometabolism can be present in young adults in their 20s.[13] We suggest that a vicious cycle can gradually develop in which latent presymptomatic brain glucose hypometabolism can lead to chronic brain energy deprivation, deteriorating neuronal function, further decline in demand for glucose, and further cognitive decline (Fig. 1).[1]

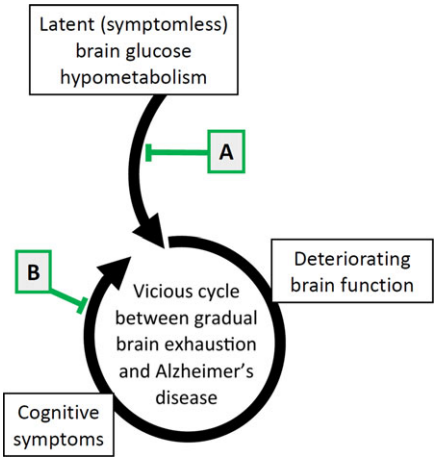

Figure 1. Latent brain glucose hypometabolism contributes to the development of a vicious cycle of accelerating metabolic deterioration and neuronal dysfunction, thereby increasing the risk of Alzheimer's disease (AD). Controlled clinical trials with ketogenic supplements are in progress and aim to bypass glucose hypometabolism and delay cognitive decline at (A) the very early stage of AD (i.e., mild cognitive impairment) or (B) later when the disease is more established.

The presence of presymptomatic brain glucose hypometabolism does not necessarily make it the primary cause of AD or indicate that neuronal function is necessarily still normal, nor even that glucose hypometabolism is the first abnormality detectable in those at risk of AD. Nevertheless, cognitive outcomes suggest that the brains of some older people can resist inadequate brain glucose supply for a considerable time.[15,17] Knowing that brain glucose hypometabolism can be present in people at risk of AD but before the onset of measurable clinical (cognitive) deficits has implications for potential therapeutic strategies.[1,19–21]

Ketones: the brain's physiological alternative fuel to glucose

The now classic studies by Owen *et al.*[22] and Drenick *et al.*[23] demonstrated that ketones are the main

reserve fuel for the brain when glucose supply is severely compromised by medically supervised starvation lasting 40 or even 60 days, respectively. The liver can produce ketones at a rate of 100–150 g/day,[24,25] which is sufficient to meet the brain's ketone utilization during starvation. The energy cost to the liver of producing ketones is supplied by gluconeogenesis (mostly in the kidney), the rate of which parallels and may eventually limit maximum achievable ketone production.[24,26]

In adults, ketogenesis is principally from long-chain fatty acids (mostly 16 and 18 carbons) stored in adipose tissue, the release of which is controlled by insulin. The branched-chain amino acids, valine, isoleucine, and leucine, are also ketogenic, with much of the amino acid catabolism occurring in skeletal muscle. During fasting, blood glucose and insulin decrease, which releases the inhibition on lipolysis in adipose tissue, permitting increased release of free fatty acids. The increase in plasma free fatty acids helps meet the need for an alternative fuel to glucose for most organs with the notable exception of the brain. The increased supply of free fatty acids entering the liver leads to fatty acid beta oxidation and ketogenesis due to condensation of pairs of acetyl CoA units as their availability exceeds their utilization by the tricarboxylic acid cycle.[27] Ketones produced by the liver cannot be catabolized by the liver and are released into the circulation. As far as is known, all organs can potentially use ketones as fuel but, in practice, as fasting or starvation becomes prolonged, skeletal muscle consumes progressively less ketones, and they are used principally by the brain.[18]

Insulin sensitivity is an important parameter in ketogenesis because it controls the rise and fall of plasma glucose and free fatty acids. Indeed, conditions involving decreased insulin sensitivity (e.g., insulin resistance) impair tissue glucose uptake and become associated with a vicious cycle of hyperglycemia, hyperinsulinemia, and an eventual trend toward type 2 diabetes, which is a major risk factor for AD.[28,29] Postprandial hyperinsulinemia normally inhibits fatty acid release from adipose tissue and, hence, ketogenesis, but only as long as insulin sensitivity and tissue glucose uptake are normal (i.e., if insulin returns to baseline 2–3 h postprandially). Sedentary lifestyles and excessive intake of simple sugars commonly lead to slower insulin clearance and chronic hyperinsulinemia, which compromise not only tissue glucose metabolism but also ketogenesis and ketone catabolism.[30] Hyperinsulinemia therefore puts the aging brain in double jeopardy, in part because the brain is then acquiring/utilizing less glucose but also because less of the main alternative fuel, ketones, is being produced.[1,31,32]

Regional brain ketone uptake in early AD

We have compared brain glucose (FDG) and ketone (^{11}C–AcAc) uptake using PET in early AD.[33] Our aim was threefold—to verify earlier reports that AD patients had normal ketone but low brain glucose uptake,[34] to assess brain fuel metabolism in early AD rather than in the more advanced stages previously reported,[35] and to quantify the regional pattern of brain uptake of both fuels in AD under postprandial conditions. As expected, global brain FDG uptake was 14% lower in early AD patients compared to cognitively normal age-matched controls. This global glucose deficit was primarily confined to the parietal cortex, posterior cingulate, and thalamus.[33] However, neither net ^{11}C–AcAc uptake nor the rate constant for AcAc uptake were significantly different in the brain as a whole or in any brain region in AD versus controls.[33] The kinetics of ketone PET tracer metabolism in the brain (whether ^{11}C–AcAc or ^{11}C–β-HB[36]) suggest a one-compartment model in which there is essentially no tissue ketone accumulation because utilization matches uptake. Hence, plasma AcAc or β-HB are highly positively correlated to their respective utilization by the brain. Furthermore, the slope of this relationship does not appear to differ between controls and early AD,[33] at least when plasma ketones are relatively low and supplying less than 5% of brain energy requirements (Fig. 2). These results confirm the earlier studies of both Lying-Tunell *et al.*[35] and Ogawa *et al.*[34] ^{11}C–AcAc is chemically identical to AcAc produced by the body; therefore, unlike with FDG, which is taken up by the plasma membrane but not metabolized beyond hexokinase, it is possible to interpret our results as showing that both brain uptake and metabolism of ketones were normal in early AD. Ketone uptake into the brain occurs through monocarboxylate transporters, which are distinct from glucose transporters. Hence, brain cells in AD still have functional ketone uptake and metabolism and so the problem with glucose uptake/metabolism appears to be specific to glucose. Like glucose, ketones function as more than

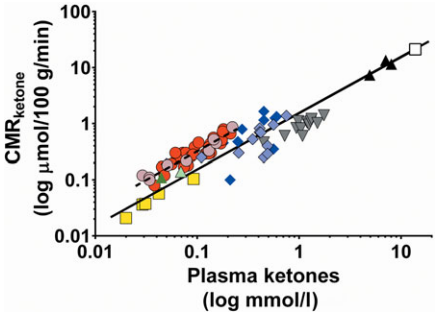

Figure 2. Direct, linear relation between plasma ketone concentration and brain ketone uptake in adults. Two relationships are shown, one for plasma β-hydroxybutyrate (β-HB) versus the rate of brain β-HB uptake (solid line, $R^2 = 0.97$; $Y = 1.57X - 0.20$; $P < 0.0001$), and the other for plasma acetoacetate (AcAc) versus the rate of brain AcAc uptake[33] (dotted line, $R^2 = 0.83$; $Y = 3.46X - 0.03$; $P < 0.0001$): ● Alzheimer's disease (AD); ● healthy age-matched controls. Units are the same for both ketones and cerebral metabolic rate (CMR; µmol/100 g/min). β-HB data have been combined from several sources: □ postprandial state,[36] ▼ β-HB infusion,[68] ◆ AD; and ◆ healthy older controls,[35] ▲ 40-day fast,[22] □ 60-day fast,[23] and △ AD and ▲ healthy older controls.[34] All the β-HB data are from arteriovenous difference studies, except for one report that used β-HB-PET.[36] The AcAc data were obtained using ^{11}C–AcAc PET.[33] Each symbol represents a single individual except when not available in the original publication: Drenick *et al.*[23] in which □ represents a mean of $n = 5$ participants and Ogawa *et al.*[34] in which △ and ▲ both represent a mean of $n = 7$. The relationship between plasma β-HB and the percentage of brain energy consumption supplied by β-HB in adults is as follows: at plasma β-HB values around 0.1 mM, ketones supply over 5% of brain energy; at 1 mM β-HB, they supply about 10–15%; at 5–7 mM β-HB, 50–65%; and at over 7–8 mM β-HB, over 75% of brain energy consumption. For a given plasma AcAc concentration, AcAc is taken up by the brain more rapidly than β-HB, which is why the dotted regression line lies above that of the solid line for β-HB.

just cellular fuels, so the latter may be beneficial for the AD brain because of effects other than replacing glucose as a fuel, including supporting glutamatergic function.[4,37]

Like glucose, ketones generate ATP by oxidative phosphorylation in mitochondria. However, unlike glucose—which can also be metabolized by aerobic glycolysis producing lactate, which, in turn, also generates some ATP in the cytosol—ketones generate ATP uniquely via oxidative phosphorylation. Normal brain ketone metabolism in early AD indirectly supports the speculation that oxidative phosphorylation must still be normal in early AD,[38] because otherwise normal ketone catabolism could not be maintained. These observations provide a rationale for the concept that the fuel hypometabolism in the AD brain is specific to glucose. Hence, providing the aging brain with more ketones may help it overcome the creeping deficit in glucose uptake and metabolism, thereby delaying brain energy exhaustion and decreasing the risk of AD (Fig. 1).

Ketogenesis from medium-chain triglycerides: dose–response relationship

Fasting or very low carbohydrate intake induces ketosis because long-chain fatty acids are beta oxidized by the liver. In adults, most dietary and hence most adipose tissue long-chain fatty acids are of 16 or 18 carbons in length. However, breast milk contains medium-chain fatty acids (i.e., fatty acids of 6–12 carbons). Without resorting to fasting or starvation, breastfed infants achieve relatively sustained but mild ketosis by metabolizing medium-chain fatty acids as they are provided from breastmilk.[39] Medium-chain fatty acids are mostly absorbed through the portal vein, hence gaining direct access to the liver without first going through the peripheral circulation. They are also beta oxidized without needing to be activated by carnitine, the net result of which is more rapid ketogenesis from medium-chain than from long-chain fatty acids.

With a couple of exceptions, there is normally no opportunity to consume medium-chain fatty acids from the diet once breastfeeding has been terminated. The exceptions are coconut oil and palm kernel oil, in which the most ketogenic medium-chain fatty acids, octanoic (caprylic) and decanoic (capric), make up approximately 9% and 10% of the fatty acids, respectively. The fraction of these oils that contain medium-chain fatty acids can be concentrated, resulting in the generic ketogenic product medium-chain triglyceride (MCT).[39,40] The ratio of these two ketogenic fatty acids and their proportion of the total can vary widely from one MCT product to another. Notwithstanding the generic nature of MCTs and different study designs to assess their metabolism, there is a remarkably strong positive correlation between the maximal plasma ketone (β-HB) level achieved and the oral dose of MCTs over a range of 10–70 g ($R^2 = 0.97$; $P < 0.0001$). Hence, a 30-g oral dose of MCTs results in a maximal plasma β-HB of approximately

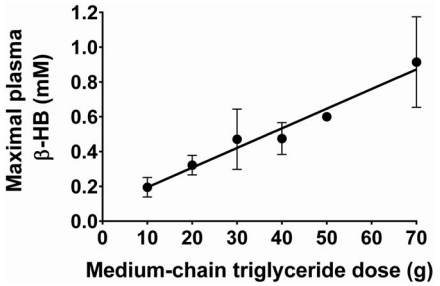

Figure 3. Direct relationship between dose of medium-chain triglyceride and maximal observed plasma β-hydroxybutyrate (β-HB) ($Y = 0.01X + 0.08$; $R^2 = 0.97$; $P < 0.0001$). Data were collated by dose from several human studies in which MCTs were given as single or multiple oral doses.[40,42,46,47,54,69,70] The exact composition or source of the MCTs used in these studies was not always stated in the original papers but is usually predominantly a mixture of octanoate and decanoate. However, the ratio of octanoate to decanoate can vary from 1:2 to 2:1.

0.5 mM, and a 70-g dose raises plasma β-HB to approximately 1.0 mM (Fig. 3). These dose–response studies show similar results whether single or multiple doses of MCTs are given, probably because of rapid plasma ketone clearance.

Healthy older people metabolize ketones to CO_2 at the same rate as younger adults.[40] Indeed, hyperketonemia after 18 h of fasting may actually be somewhat higher in the seventh to eighth decade of life compared to younger adults.[41] Hence, the capacity to produce and use ketones may actually be increasing somewhat during healthy aging. These studies did not distinguish between ketone utilization by the brain versus other organs, but our brain ketone PET studies confirm that the brain has similar ketone uptake and utilization in healthy older compared to younger persons[15] (Fig. 2).

Experimental hyperketonemia in conditions of acute or chronic cognitive deficit

Oral MCTs have been shown to improve cognitive outcomes during controlled experimental hypoglycemia caused by insulin infusion.[42] The very high-fat ketogenic diet has been reported to have a similar beneficial effect on cognitive and cardiovascular outcomes in MCI, the prodromal state to AD.[43] These reports complement the studies showing that autonomic and neurological symptoms of severe experimental hypoglycemia as low as 0.5 mM induced by insulin infusion can be avoided by ketone infusion[44,45] or prolonged medically supervised starvation.[18] They demonstrate that ketones can sustain normal brain function even when plasma glucose is severely reduced. Several products based on MCTs are now available on the market or by prescription in the United States and Europe. The arrival of these products was greatly facilitated by reports that MCTs had beneficial effects on cognitive outcomes in mild-to-moderate AD after a single dose[46] or with regular consumption over several months.[47]

AcAc and β-HB can also be administered orally or by infusion as salts or esters,[48–50] with the esters being more practical for long-term use because they avoid the issues of cation overload. The safety of a β-HB monoester[50] and its utility in improving some aspects of cognitive function in a single case history of early-onset AD have recently been reported.[51] The results of these clinical studies are still preliminary but they support the hypothesis that a brain glucose deficit could be contributing to impaired cognition associated with aging and that this brain fuel deficit can at least in part be bypassed by a source of ketones, whether it be a ketogenic supplement containing MCTs, a ketone ester, or a very high-fat ketogenic diet.

Safety of medium-chain triglycerides

MCTs in doses up to 1 g/kg/day have a robust safety record in all species studied, including humans.[52,53] Nevertheless, MCTs can have secondary side effects involving gastrointestinal distress, an issue that can be partially mitigated by gradual dose titration. MCTs are saturated fats and, as such, have long been assumed to increase cardiovascular risk factors and body weight. However, treatment for 30 days with 30 g/day of MCTs does not adversely affect body weight, body fat content, or body mass index, nor does it affect serum glucose, insulin, triglycerides, cholesterol, or free fatty acids.[54]

Perspectives and challenges requiring further work

We propose that AD is, in part, a product of chronic gradual brain energy starvation or exhaustion due specifically to an increasing deficit in brain glucose uptake and metabolism. In addition to the fuel deficit in the brain, neuroinflammation mediated by free radical damage may be exacerbated by impaired brain glucose uptake because glucose normally contributes to the synthesis of antioxidants via the pentose phosphate

pathway.[55,56] Owing to mild insulin resistance associated with aging,[57,58] replacement of declining glucose transport into the brain by ketones produced endogenously from fatty acids in adipose tissue is also inefficient.

Several clinical studies suggest that the early stages of AD may be amenable to nutritional treatments that raise plasma ketones.[46,47] Our PET results showing normal brain ketone uptake early in AD but low brain glucose uptake also support the plausibility of using a "keto-neurotherapeutic" strategy in early AD. The broadly similar neurological/cognitive benefit of a very high-fat ketogenic diet containing no MCTs,[43] or a typical diet containing over 50% carbohydrate to which MCTs or ketone esters are added,[51] suggests that the improvement in cognition is related to a common denominator of raised plasma ketones, which bypass chronically impaired glucose uptake and utilization by the AD brain. However, this is still speculative; to date, no study has provided a direct mechanism by which MCTs or ketones could improve cognitive outcomes. Moderate ketosis may stimulate mitochondrial biogenesis,[59] which may also help improve oxidative phosphorylation and ATP generation in the brain. It has not yet been established whether certain MCTs (e.g., octanoate, decanoate, or others) are more effective for ketogenesis than others. Octanoic acid can be taken up and consumed as a fuel by the brain;[60,61] therefore, it may have direct effects on brain function, including but not limited to conversion to ketones by astrocytes.[62] Ketones do not contribute to anaplerosis (replacement of tricarboxylic acid cycle intermediates), so whether the benefit of prolonged ketosis could be self-limiting remains to be seen.[63,64] Specific processes in the brain may need glycolysis-derived ATP but this remains quite controversial,[65–67] and if confirmed, would be a function that glucose, but not ketones, could support.

Several clinical trials registered on ClinicalTrials.gov are underway that combine either a ketogenic supplement or diet with cognitive evaluation and should produce results over the next 2–3 years. These studies should be able to shed further light on the potential utility of keto-therapeutics in neurodegenerative diseases such as AD.

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Conflicts of interest

The authors declare no conflicts of interest.

References

1. Cunnane, S. *et al.* 2011. Brain fuel metabolism, aging, and Alzheimer's disease. *Nutrition* **27:** 3–20.
2. Terry, R.D. *et al.* 1991. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Ann. Neurol.* **30:** 572–580.
3. Musa-Veloso, K. *et al.* 2006. Breath acetone predicts plasma ketone bodies in children with epilepsy on a ketogenic diet. *Nutrition* **22:** 1–8.
4. Hertz, L., Y. Chen & H.S. Waagepetersen. 2015. Effects of ketone bodies in Alzheimer's disease in relation to neural hypometabolism, beta-amyloid toxicity, and astrocyte function. *J. Neurochem.* **134:** 7–20.
5. VanItallie, T.B. 2015. Biomarkers, ketone bodies, and the prevention of Alzheimer's disease. *Metabolism* **64:** S51–S57.
6. Scholl, M. *et al.* 2011. Time course of glucose metabolism in relation to cognitive performance and postmortem neuropathology in Met146Val PSEN1 mutation carriers. *J. Alzheimers Dis.* **24:** 495–506.
7. Fox, N.C. *et al.* 1997. Clinicopathological features of familial Alzheimer's disease associated with the M139V mutation in the presenilin 1 gene. Pedigree but not mutation specific age at onset provides evidence for a further genetic factor. *Brain* **120**(Pt 3): 491–501.
8. Blennow, K., M.J. de Leon & H. Zetterberg. 2006. Alzheimer's disease. *Lancet* **368:** 387–403.
9. Kennedy, A.M. *et al.* 1995. Deficits in cerebral glucose metabolism demonstrated by positron emission tomography in individuals at risk of familial Alzheimer's disease. *Neurosci. Lett.* **186:** 17–20.
10. Mosconi, L. *et al.* 2005. Reduced hippocampal metabolism in MCI and AD: automated FDG-PET image analysis. *Neurology* **64:** 1860–1867.
11. Reiman, E.M. *et al.* 2004. Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. *Proc. Natl. Acad. Sci. U.S.A.* **101:** 284–289.
12. Bu, G. 2009. Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. *Nat. Rev. Neurosci.* **10:** 333–344.
13. Castellano, C.A. *et al.* 2015. Regional brain glucose hypometabolism in young women with polycystic ovary syndrome: possible link to mild insulin resistance. *PLoS One* **10:** e0144116.
14. Velliquette, R.A., T. O'Connor & R. Vassar. 2005. Energy inhibition elevates beta-secretase levels and activity and is potentially amyloidogenic in APP transgenic mice: possible early events in Alzheimer's disease pathogenesis. *J. Neurosci.* **25:** 10874–10883.

15. Nugent, S. *et al.* 2014. Brain glucose and acetoacetate metabolism: a comparison of young and older adults. *Neurobiol. Aging* **35:** 1386–1395.
16. Nugent, S. *et al.* 2014. Glucose hypometabolism is highly localized but lower cortical thickness and brain atrophy are widespread in cognitively normal older adults. *Am. J. Physiol. Endocrinol. Metab.* **306:** E1315–E1321.
17. Nugent, S. *et al.* 2015. Relationship of metabolic and endocrine parameters to brain glucose metabolism in older adults: do cognitively-normal older adults have a particular metabolic phenotype? *Biogerontology*. DOI 10.1007/s10522-015-9595-7.
18. Kalpouzos, G. *et al.* 2009. Voxel-based mapping of brain gray matter volume and glucose metabolism profiles in normal aging. *Neurobiol. Aging* **30:** 112–124.
19. Gibson, R.E. *et al.* 2000. Non-invasive radiotracer imaging as a tool for drug development. *Curr. Pharm. Des.* **6:** 973–989.
20. Veech, R.L. *et al.* 2001. Ketone bodies, potential therapeutic uses. *IUBMB Life* **51:** 241–247.
21. Blass, J.P. 2008. A new approach to treating Alzheimer's disease. *Ann. N.Y. Acad. Sci.* **1147:** 122–128.
22. Owen, O.E. *et al.* 1967. Brain metabolism during fasting. *J. Clin. Invest.* **46:** 1589–1595.
23. Drenick, E.J. *et al.* 1972. Resistance to symptomatic insulin reactions after fasting. *J. Clin. Invest.* **51:** 2757–2762.
24. Flatt, J.P. 1972. On the maximal possible rate of ketogenesis. *Diabetes* **21:** 50–53.
25. Reichard, G.A., Jr. *et al.* 1974. Ketone-body production and oxidation in fasting obese humans. *J. Clin. Invest.* **53:** 508–515.
26. Garber, A.J. *et al.* 1974. Hepatic ketogenesis and gluconeogenesis in humans. *J. Clin. Invest.* **54:** 981–989.
27. Hashim, S.A., A. Arteaga & T.B. Van Itallie. 1960. Effect of a saturated medium-chain triglyceride on serum-lipids in man. *Lancet* **1:** 1105–1108.
28. Craft, S. 2009. The role of metabolic disorders in Alzheimer disease and vascular dementia: two roads converged. *Arch. Neurol.* **66:** 300–305.
29. Baker, L.D. *et al.* 2011. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. *Arch. Neurol.* **68:** 51–57.
30. Fukao, T., G.D. Lopaschuk & G.A. Mitchell. 2004. Pathways and control of ketone body metabolism: on the fringe of lipid biochemistry. *Prostaglandins Leukot. Essent. Fatty Acids* **70:** 243–251.
31. Henderson, S.T. 2008. Ketone bodies as a therapeutic for Alzheimer's disease. *Neurotherapeutics* **5:** 470–480.
32. Mamelak, M. 2012. Sporadic Alzheimer's disease: the starving brain. *J. Alzheimers Dis.* **31:** 459–474.
33. Castellano, C.A. *et al.* 2015. Lower brain ^{18}F-fluorodeoxyglucose uptake but normal ^{11}C-acetoacetate metabolism in mild Alzheimer's disease dementia. *J. Alzheimers Dis.* **43:** 1343–1353.
34. Ogawa, M. *et al.* 1996. Altered energy metabolism in Alzheimer's disease. *J. Neurol. Sci.* **139:** 78–82.
35. Lying-Tunell, U. *et al.* 1981. Cerebral blood flow and metabolic rate of oxygen, glucose, lactate, pyruvate, ketone bodies and amino acids. *Acta Neurol. Scand.* **63:** 337–350.
36. Blomqvist, G. *et al.* 1995. Use of R-beta-[1-11C] hydroxybutyrate in PET studies of regional cerebral uptake of ketone bodies in humans. *Am. J. Physiol.* **269:** E948–E959.
37. Roy, M. *et al.* 2015. Rapid adaptation of rat brain and liver metabolism to a ketogenic diet: an integrated study using (1)H- and (13)C-NMR spectroscopy. *J. Cereb. Blood Flow Metab.* **35:** 1154–1162.
38. Hoyer, S., K. Oesterreich & O. Wagner. 1988. Glucose metabolism as the site of the primary abnormality in early-onset dementia of Alzheimer type? *J. Neurol.* **235:** 143–148.
39. Cunnane, S.C. & M.A. Crawford. 2014. Energetic and nutritional constraints on infant brain development: implications for brain expansion during human evolution. *J. Hum. Evol.* **77:** 88–98.
40. Freemantle, E. *et al.* 2009. Metabolic response to a ketogenic breakfast in the healthy elderly. *J. Nutr. Health Aging* **13:** 293–298.
41. London, E.D. *et al.* 1986. Effects of fasting on ketone body concentrations in healthy men of different ages. *J. Gerontol.* **41:** 599–604.
42. Page, K.A. *et al.* 2009. Medium-chain fatty acids improve cognitive function in intensively treated type 1 diabetic patients and support in vitro synaptic transmission during acute hypoglycemia. *Diabetes* **58:** 1237–1244.
43. Krikorian, R. *et al.* 2012. Dietary ketosis enhances memory in mild cognitive impairment. *Neurobiol. Aging* **33:** 425.e19–27.
44. Amiel, S.A. *et al.* 1991. Ketone infusion lowers hormonal responses to hypoglycaemia: evidence for acute cerebral utilization of a non-glucose fuel. *Clin. Sci. (Lond.)* **81:** 189–194.
45. Veneman, T. *et al.* 1994. Effect of hyperketonemia and hyperlacticacidemia on symptoms, cognitive dysfunction, and counterregulatory hormone responses during hypoglycemia in normal humans. *Diabetes* **43:** 1311–1317.
46. Reger, M.A. *et al.* 2004. Effects of beta-hydroxybutyrate on cognition in memory-impaired adults. *Neurobiol. Aging* **25:** 311–314.
47. Henderson, S.T. *et al.* 2009. Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial. *Nutr. Metab. (Lond.)* **6:** 31.
48. Plecko, B. *et al.* 2002. Oral beta-hydroxybutyrate supplementation in two patients with hyperinsulinemic hypoglycemia: monitoring of beta-hydroxybutyrate levels in blood and cerebrospinal fluid, and in the brain by in vivo magnetic resonance spectroscopy. *Pediatr. Res.* **52:** 301–306.
49. Hasselbalch, S.G. *et al.* 1996. Changes in cerebral blood flow and carbohydrate metabolism during acute hyperketonemia. *Am. J. Physiol.* **270:** E746–E751.
50. Clarke, K. *et al.* 2012. Kinetics, safety and tolerability of (R)-3-hydroxybutyl (R)-3-hydroxybutyrate in healthy adult subjects. *Regul. Toxicol. Pharmacol.* **63:** 401–408.
51. Newport, M.T. *et al.* 2015. A new way to produce hyperketonemia: use of ketone ester in a case of Alzheimer's disease. *Alzheimers Dement.* **11:** 99–103.
52. Bach, A.C. & V.K. Babayan. 1982. Medium-chain triglycerides: an update. *Am. J. Clin. Nutr.* **36:** 950–962.
53. Traul, K.A. *et al.* 2000. Review of the toxicologic properties of medium-chain triglycerides. *Food Chem. Toxicol.* **38**: 79–98.

54. Courchesne-Loyer, A. *et al.* 2013. Stimulation of mild, sustained ketonemia by medium-chain triacylglycerols in healthy humans: estimated potential contribution to brain energy metabolism. *Nutrition* **29:** 635–640.
55. Jiang, P., W. Du & M. Wu. 2014. Regulation of the pentose phosphate pathway in cancer. *Protein Cell* **5:** 592–602.
56. Bolanos, J.P. & A. Almeida. 2010. The pentose-phosphate pathway in neuronal survival against nitrosative stress. *IUBMB Life* **62:** 14–18.
57. Rowe, J.W. *et al.* 1983. Characterization of the insulin resistance of aging. *J. Clin. Invest.* **71:** 1581–1587.
58. Stout, R.W. 1994. Glucose tolerance and ageing. *J. R. Soc. Med.* **87:** 608–609.
59. Bough, K.J. *et al.* 2006. Mitochondrial biogenesis in the anticonvulsant mechanism of the ketogenic diet. *Ann. Neurol.* **60:** 223–235.
60. Ebert, D., R.G. Haller & M.E. Walton. 2003. Energy contribution of octanoate to intact rat brain metabolism measured by ^{13}C nuclear magnetic resonance spectroscopy. *J. Neurosci.* **23:** 5928–5935.
61. Kuge, Y. *et al.* 1995. Brain uptake and metabolism of [1–11C]octanoate in rats: pharmacokinetic basis for its application as a radiopharmaceutical for studying brain fatty acid metabolism. *Ann. Nucl. Med.* **9:** 137–142.
62. Auestad, N. *et al.* 1991. Fatty acid oxidation and ketogenesis by astrocytes in primary culture. *J. Neurochem.* **56:** 1376–1386.
63. Mochel, F. *et al.* 2005. Pyruvate carboxylase deficiency: clinical and biochemical response to anaplerotic diet therapy. *Mol. Genet. Metab.* **84:** 305–312.
64. Brunengraber, H. & C.R. Roe. 2006. Anaplerotic molecules: current and future. *J. Inherit. Metab. Dis.* **29:** 327–331.
65. Vaishnavi, S.N. *et al.* 2010. Regional aerobic glycolysis in the human brain. *Proc. Natl. Acad. Sci. U.S.A.* **107:** 17757–17762.
66. Dienel, G.A. 2012. Brain lactate metabolism: the discoveries and the controversies. *J. Cereb. Blood Flow Metab.* **32:** 1107–1138.
67. Hyder, F. *et al.* 2013. Glutamatergic function in the resting awake human brain is supported by uniformly high oxidative energy. *J. Cereb. Blood Flow Metab.* **33:** 339–347.
68. Blomqvist, G. *et al.* 2002. Effect of acute hyperketonemia on the cerebral uptake of ketone bodies in nondiabetic subjects and IDDM patients. *Am. J. Physiol. Endocrinol. Metab.* **283:** E20–E28.
69. Seaton, T.B. *et al.* 1986. Thermic effect of medium-chain and long-chain triglycerides in man. *Am. J. Clin. Nutr.* **44:** 630–634.
70. Pi-Sunyer, F.X., S.A. Hashim & T.B. Van Itallie. 1969. Insulin and ketone responses to ingestion of medium and long-chain triglycerides in man. *Diabetes* **18:** 96–100.