A Review of Ketogenic Therapies for Alzheimer's Disease

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Abstract

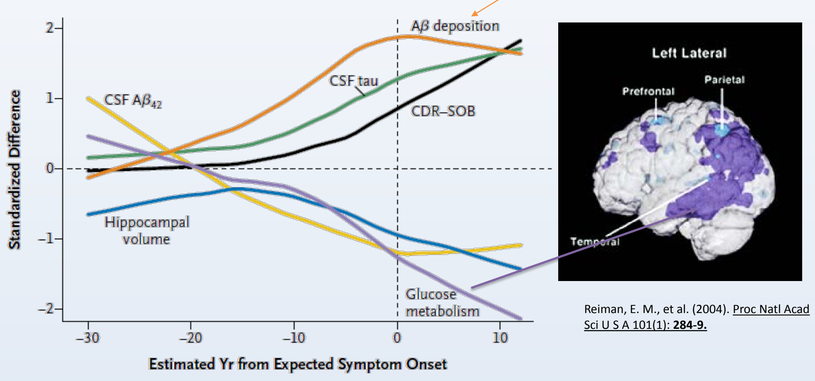
Objectives: A review of results from studies of ketogenic diets and exogenous induction of ketosis in Alzheimer's disease will be presented.
Introduction: Alzheimer's disease (AD) is an age-associated neurodegenerative disease characterized by accumulation of aggregated amyloid-beta in the cerebral cortex and hippocampus and regional declines in the cerebral metabolic rate of glucose (CMRglc) in the parietal, temporal, frontal, and posterior cingulate cortices. The reduction in CMRglc begins early and correlates with declines in cognitive function. Glucose hypometabolism is frequently attributed to cell and synaptic loss. However, arterio-venous sampling studies in AD patients have demonstrated that while glucose extraction is decreased in AD, oxygen consumption is relatively intact, suggesting a switch in the AD brain from metabolism of glucose to other substrates. Unlike other organs in the body, the brain does not efficiently metabolize fats and is normally dependent on large amounts of glucose for proper function. However, under conditions of low glucose availability, such as extended fasting, the body will mobilize fat reserves for hepatic conversion to ketone bodies, which can fuel up to 60% of the brain's energy requirements. Ketone bodies are not just a fuel source, but also act as signaling metabolites with demonstrated neuroprotective and metabolic health properties that act through anti-inflammatory and gene expression pathways. Recent positron emission tomography (PET) studies comparing age matched controls to AD patients have found reductions CMRglc in AD while the cerebral metabolic rate of the ketone body acetoacetate (CMRaca) remains intact, indicating that the metabolic defect is specific to glucose and suggesting the supplementation with ketone bodies can improve overall metabolic rate.
Methods: Ketosis can be induced by dietary manipulation as well as by exogenous induction by ketogenic compounds. Several studies have examined the cognitive effects of ketogenic diets in AD and results of those studies will be reviewed. Other studies have examined the use of ketogenic compounds in patients with mild and mild-to-moderate AD. Multiple studies have examined the effect of ketosis on overall cerebral metabolic rate as well as cognitive function. Results of these studies will be presented and reviewed.
Results: Small studies of ketogenic diets have demonstrated improvement in measures of cognitive function in both mild and mild-to-moderate AD patients. Similarly, we have used a ketone inducing compound known as tricaprilin to exogenously induce ketosis without dietary change in mild-to-moderate AD patients. In both acute and 90-day dosing, the induction of ketosis demonstrated improvement in cognitive performance, particularly in subjects who are non-carriers of the epsilon 4 allele of the apolipoprotein E gene (APOE4). Carriage status of APOE4 is the major genetic risk factor for the most common form of AD (sporadic AD). In addition, the improvements in cognitive performance after tricaprilin administration correlated with circulating ketone body concentrations, suggesting that ketosis was responsible for the improvement in cognition.
Conclusion: Ketone based therapies are an area of growing interest for patients with AD and offer hope for new treatment paradigms.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that primarily affects the elderly. The disease typically begins with deficits in short-term memory (amnesia). As the disease progresses, symptoms may include problems with language (aphasia), disorientation (including easily getting lost), and behavioral issues. Gradually, bodily functions are lost, ultimately leading to death. There are few treatment options for patients with AD.

Pathology

Accumulation of aggregated amyloid-beta and neurofibrillary tangles (NFTs) in the cerebral cortex and hippocampus.



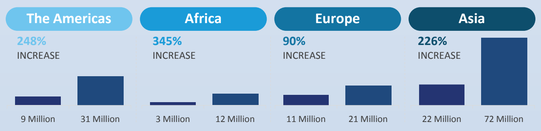
Reiman, E. M., et al. (2004). Proc Natl Acad Sci U S A 101(1): **284-9.**

Genetic Risk Factors

- Carriage status of the epsilon 4 variant of the lipid transport gene apolipoprotein E (APOE4).
- Individuals that carry one APOE4 allele are at about a 3 fold increased risk of developing AD, while those that carry two copies are at about a 12 fold increased risk.

Unmet Medical Need

- The global number of people with dementia will triple between 2013 and 2050
- Much of the increase will be in low and middle income countries



Drug Development

Most drugs in development for AD have targeting β-Amyloid and more recently tau.

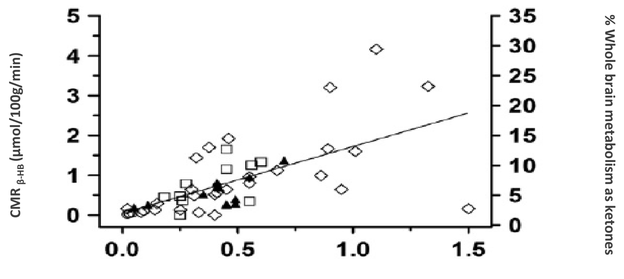
- During 2002 to 2012, the success rate for advancing new agents for regulatory approval was 0.4% (Failure rate of 99.6%). Compare with success rate in oncology of 19%*
- During 2007 to 2017, the success rate for advancing new agents for regulatory approval was 0% (Failure rate of 100%)
- A growing need for mechanistic diversity in AD drug development is warranted

*Cummings, J.L., et al. (2014). Alzheimer's disease drug-development pipeline: Few candidates, frequent failures. Alzheimer's Res Ther 6, 37.

Rationale

Brain Ketone Body Metabolism

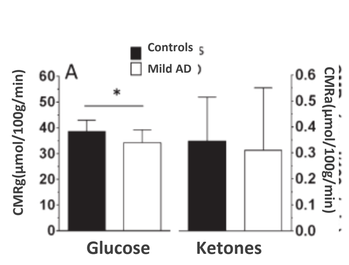
Ketones are used in a concentration dependent manner by the brain



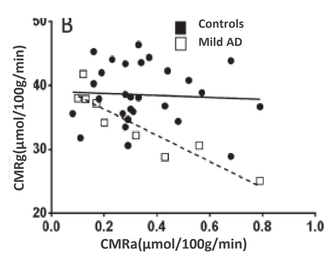
Cunnane, S. et al. (2011). "Brain fuel metabolism, aging, and Alzheimer's disease." Nutrition 27(1): 3-20.

AD Brain has Switched Metabolism to Ketones

Arterio-venous sampling studies in AD patients have demonstrated that cerebral metabolic rate of glucose (CMRglc) is decreased relative to healthy aged controls, while oxygen consumption is relatively intact, suggesting a switch in the AD brain from glucose to ketone body metabolism.



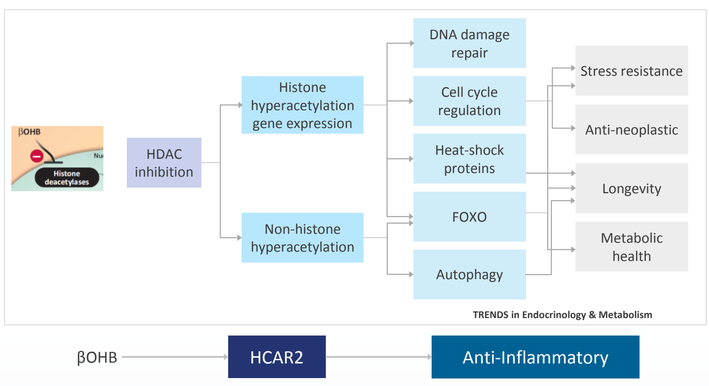
Defect is specific to glucose



In AD patients Lower CMRg = Higher CMRa

Castellano, C.A., Nugent, S., Paquet, N., Tremblay, S., Bocti, C., Lacombe, G., Imbeault, H., Turcotte, E., Fulop, T., and Cunnane, S.C. (2014). Lower Brain 18F-Fluorodeoxyglucose Uptake But Normal 11C-Acetoacetate Metabolism in Mild Alzheimer's Disease Dementia. J Alzheimer's Dis.

Ketone Bodies are Neuroprotective



Newman, J.C., and Verdin, E. **(2014)**. Ketone bodies as signaling metabolites. *Trends Endocrinol Metab 25, **42-52.***

Results

Ketogenic Diets (KD) in AD patients

Several studies have looked at the effects of ketogenic diets on MCI or AD patients

KD Improved Cognitive Performance in Mild AD

Krikorian et al 2012 studied 23 MCI subjects on a low carbohydrate diet versus a high carbohydrate diet

- Verbal memory improved (p=0.01)
- Weight reduced (p<0.0001)
- Fasting glucose reduced (p=0.009)
- Ketones correlated with memory performance (p=0.049)

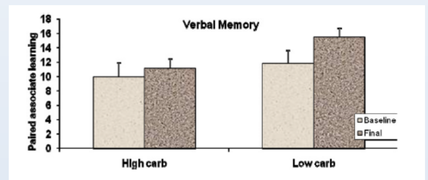
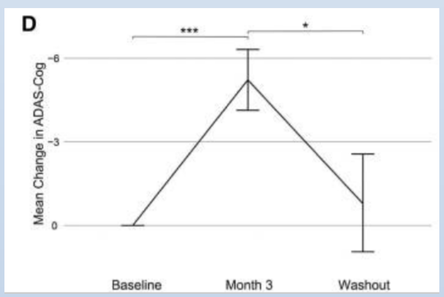


Fig. 1. Pre- and post-intervention memory performances for the low and high carbohydrate groups as measured by the Verbal Paired Associate Learning Test (Krikorian, 1996). Values are unadjusted means of the cumulative number of correct immediate recall responses summed across 4 learning trials. Vertical bars represent standard error. The analysis of covariance indicated improved learning for the low carbohydrate subjects, $F(1,20) = 6.45$, $p = 0.01$, Cohen's $f = 0.26$.

Krikorian, R., et al. (2012). "Dietary ketosis enhances memory in mild cognitive impairment." Neurobiol Aging **33**(2): 425 e419-427.

Taylor et al. 2017 studied 15 mild to moderate AD subjects were put on a very high-fat KD (VHF-KD)

- Cognition improved as measured by a mean improvement of 4.1 points on the Alzheimer's Disease Assessment Scale-cognitive subscale (P = .02) and reverted to baseline after the washout.



Taylor et al. 2018. Feasibility and efficacy data from a ketogenic diet intervention in Alzheimer's disease. Alzheimers Dement 4:28-36

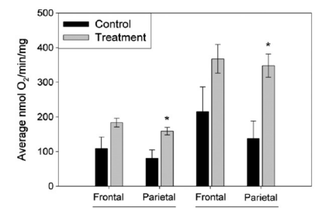
Results

Exogenous Ketosis

Animal Studies

Aged canine model of AD

Administration of tricaprilin improved mitochondrial function and cognition in aged beagles



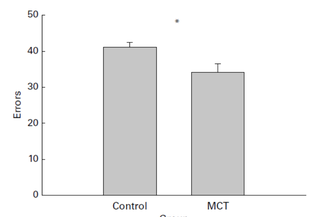


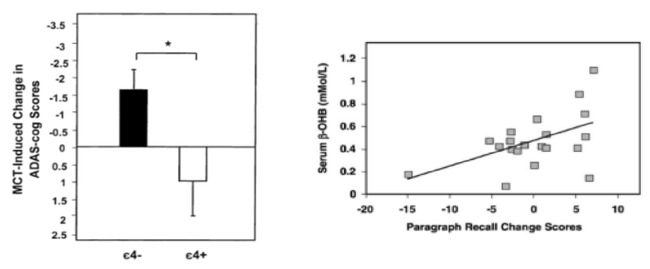
Fig. 2 – Mitochondrial respiration. The treatment animals had larger rates of state III respiration in the parietal lobes, as compared to controls (t-test, P=0.025). The treatment animals also had an increased ability to drive electrons through Complex I in the parietal lobes, as compared to controls (t-test; P=0.013). Although the trend was in the same direction in the frontal lobes, the differences were not statistically significant (t-tests, P=0.080 and P=0.115, respectively). Statistically significant differences, as compared to the control group, are indicated by an asterisk (*).

Fig. 3. Effects of dietary medium-chain TAG (MCT) supplementation on dogs' performance in complex landmark discrimination task (land-2). The data are means with their standard errors, *n* 11. The performance was expressed as total number of errors over ten sessions. * Mean values were significantly different ($P<0.05$).

1. Studzinski, C. M., W. A. Mackay, et al. (2008). "Induction of ketosis may improve mitochondrial function and decrease steady-state amyloid-beta precursor protein (APP) levels in the aged dog." Brain Res **1226: 209-17.**
2. Pan, Y., B. Larson, et al. (2010). "Dietary supplementation with medium-chain TAG has long-lasting cognition-enhancing effects in aged dogs." Br J Nutr: 1-9.

Human Studies

Reger et al. 2004 studied 20 AD subjects administered a single dose of tricaprilin results in rapid improvement in cognition



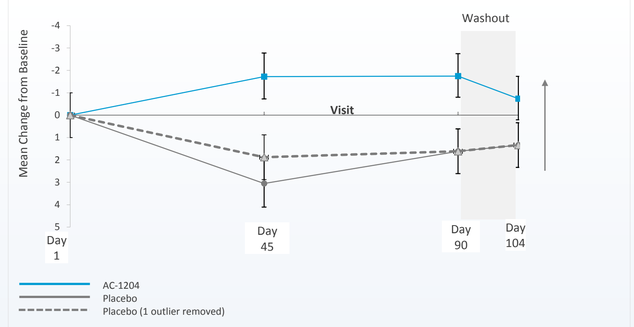
Reger et al (2004) Effects of b-hydroxybutyrate on cognition in memory-impaired adults Neurobiology of Aging. 25 (2004) 311.

Results

- AC-1202 significantly elevated serum ketone bodies
- AC-1202 significantly improved ADAS-cog in ApoE4(-) patients after single dose ($p < 0.05$)
- BHB serum levels correlated with improved memory ($p < 0.05$)

Henderson et al 2009 studied 152 AD subjects administered tricaprilin for 90 days

Change from baseline in ADAS-Cog scores in APOE4 non-carriers (a pre-specified analysis) over 90 days of administration



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.**

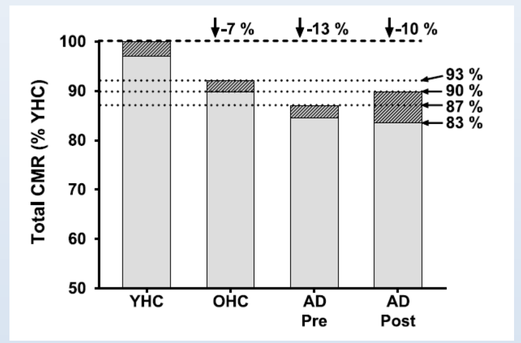
Croteau et al 2018 studied cerebral metabolism in 20 mild to moderate AD subjects given a medium chain triglyceride.

Pre-Intervention

- AD subjects cerebral metabolic of glucose was 13% lower than age matched control

Post-Intervention

- Cerebral metabolic rate of glucose did not change
- Cerebral metabolic rate of ketones increased
- Total cerebral metabolic rate increased by 3%



Croteau, E., et al. (2018). "Ketogenic Medium Chain Triglycerides Increase Brain Energy Metabolism in Alzheimer's Disease." J Alzheimers Dis **64(2): 551-561.**

Conclusions

Ketosis has the potential as a therapeutic in AD

- Alzheimer's disease is characterized by regional declines in cerebral glucose utilization
- Ketone bodies have the potential to fill the energy gap in AD
- Ketone bodies have neuroprotective properties due to their role as signaling metabolites
- Studies in aged canines demonstrate improvement in cognition and mitochondrial function
- Studies in humans demonstrate the potential to improve cognitive performance in AD patients

Limitations

Larger, long-term clinical trials are needed to demonstrate the efficacy of ketogenic treatments.

Disclosures

Cerecin is a developing ketogenic treatments for AD and other conditions.