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Hypothesis

The ketogenic diet as a potential treatment and prevention strategy for Alzheimer's disease

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ABSTRACT

The prevalence of Alzheimer's disease, a chronic neurodegenerative condition, is increasing as is the need for effective treatments and preventions. The underlying pathology of Alzheimer's is not yet fully understood, so existing research has focused on understanding the prominent features of the disease. These include amyloid plaques, which accumulate in the brains of those with Alzheimer's disease; impaired glucose metabolism; and neuronal cell death. Emerging evidence suggests that a low-carbohydrate, high-fat ketogenic diet may help to mitigate the damage associated with these pathologies. The ketogenic diet could alleviate the effects of impaired glucose metabolism by providing ketones as a supplementary energy source. In addition, this diet may help to reduce the accumulation of amyloid plaques while reversing amyloid β toxicity. Research has begun to identify early underlying mechanisms in Alzheimer's disease that could be targeted by new prevention strategies. Glycation of the ApoE protein leads to impaired transportation of important lipids, including cholesterol, to the brain, resulting in lipid deficiencies that could explain progression to the later pathologies of the disease. In this review, we hypothesize that the ketogenic diet could be an effective treatment and prevention for Alzheimer's disease, but both ketone production and carbohydrate restriction may be needed to achieve this.

Introduction

Alzheimer's disease (AD) is the leading cause of dementia, which is estimated to affect as many as 24 million people worldwide, a prevalence that is expected to double every 20 y [1]. Although there is limited understanding of the etiologic mechanisms behind AD, toxic amyloid β (Aβ) plaques and tangles in the brain are thought to cause the progression of the disease, as autopsies show that these accumulate excessively in AD brains, resulting in heightened rates of cell death [2]. For this reason, much research has focused on reducing these plaques and tangles, but further evidence now points toward neurometabolic issues as a potential underlying cause of both the plaques and tangles, and the ultimate progression of AD [3,4]. To address these metabolic issues, research has explored dietary interventions, including the high-fat, low-carbohydrate ketogenic diet (KD) [5,6]. The KD could potentially target these metabolic issues while also protecting against the Aβ plaques associated with AD. Increasingly, evidence points to a combination of genetic risk and modern dietary patterns as contributing factors in the early development of the disease. This review explores various mechanisms through which the KD could be useful in the development of treatments and prevention strategies for AD.

Glucose and ketones in AD

Impaired glucose metabolism in the brain may be one of the earliest hallmarks of AD; studies investigating young adults with a high genetic risk for AD have found that these metabolic deficits could be present as early as young adulthood, decades before the onset of dementia [7]. For this reason, detection of brain glucose hypometabolism via fluoro-2-deoxy-D-glucose positron emission tomography imaging has been suggested as an effective early diagnostic tool for AD, with studies showing 90% sensitivity in identifying AD [8]. This early impairment in glucose metabolism implies that metabolic interventions could be effective in preventing or at least inhibiting the development of the disease. It has been proposed that ketone bodies (KBs), which are produced when adhering to a KD, could be used to provide a supplementary energy supply for the brain, increasing mitochondrial efficiency and cognitive function [5,6]. This metabolic pathway involves the two KBs, β-hydroxybutyrate (β-HB) and acetoacetate, bypassing glycolysis

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to produce acetyl coenzyme A, which can then be channeled into the Kreb's cycle and thus increase energy availability in the brain (Fig. 1). Evidence suggests that brain ketone uptake is not impaired in AD in the way that glucose uptake is [5], making it a viable alternative energy precursor. This supplementary brain metabolism is the first mechanism through which the KD has been proposed to help in the treatment and prevention of AD.

Effects of KDs on Aβ plaques

In addition to modifying cellular metabolism, KBs are therapeutic in protecting against production of toxic Aβ plaques associated with AD. Van der Auwera et al. [9] fed a KD to AD model transgenic mice whereby accumulation Aβ plaques is akin to AD in humans. Results showed an elevation in serum levels of the KB β-HB, which significantly lowered total Aβ levels compared with controls. Further evidence suggests that the KD may not only reduce the accumulation of Aβ, but that KBs produced also might protect against Aβ neurotoxicity. Kashiwaya et al. [10] treated cultured rat hippocampal cells with either Aβ or β-HB or a combination of the two. Treatment with Aβ alone resulted in significantly higher levels of cell death and reduced neurite number and length compared with controls, which confirmed hippocampal neuronal Aβ toxicity. The addition of β-HB, however, reversed Aβ toxicity, acting instead as a growth factor that doubled the number of surviving cells. This demonstrates that β-HB could potentially repair existing damage. Therefore, neuroprotection against Aβ is another mechanism through which a KD may be useful for the prevention and treatment of AD.

Efficacy of ketone intervention in humans

In response to the potential of the KD as a treatment for AD, Henderson et al. [11] carried out a randomized, double-blind, placebo-controlled trial to test the effects of a ketogenic compound, AC-1202, on the cognitive function of individuals with mild to moderate AD. AC-1202 was developed as a consumable form of medium-chain triacylglycerols (MCTs) with the rationale that consumption of MCTs, which are highly ketogenic, would induce a mild state of ketosis without modifying the diets of participants. Although not a KD, AC-1202 treatment significantly elevated serum β-HB, allowing Henderson et al. to measure the effects of elevated ketones on cognitive performance. Cognitive improvement was measured as mean change from baseline on the AD Assessment Scale–Cognitive subscale (ADAS-Cog) [11,12]. Participants given AC-1202 had significantly improved ADAS-Cog scores compared with those given placebo, but only if they did not have the epsilon 4 allele of the apolipoprotein E gene, that is, they were *ApoE4*(−). Participants who did have this variant of the gene, that is, they were *ApoE4*(+), did not differ significantly from those taking placebo [11]. These results suggest that ketones may only be useful for treating AD in *ApoE4*(−) individuals; however, more detailed consideration of these findings could help to clarify the underlying mechanisms of AD pathology.

A major limitation of Henderson et al.'s study is the lack of dietary control in participants [11]. The authors state that participants were on a "normal diet," indicating no specific carbohydrate restrictions in addition to the MCT treatment. Although a MCTKD has been used as an alternative to the classic KD for the treatment of epilepsy [13], the MCTKD still involves some carbohydrate restriction [14]. The lack of carbohydrate restriction in this study could have affected results in a number of ways. Higher glucose intake inhibits ketone production [15], so the dietary carbohydrate intake of participants might limit the levels of KBs that could be achieved in the study. Furthermore, the authors of the study speculated that the lack of treatment effect in *ApoE4*(−) participants may have been due to impaired mitochondrial enzyme function or issues with insulin sensitivity. If insulin sensitivity was the

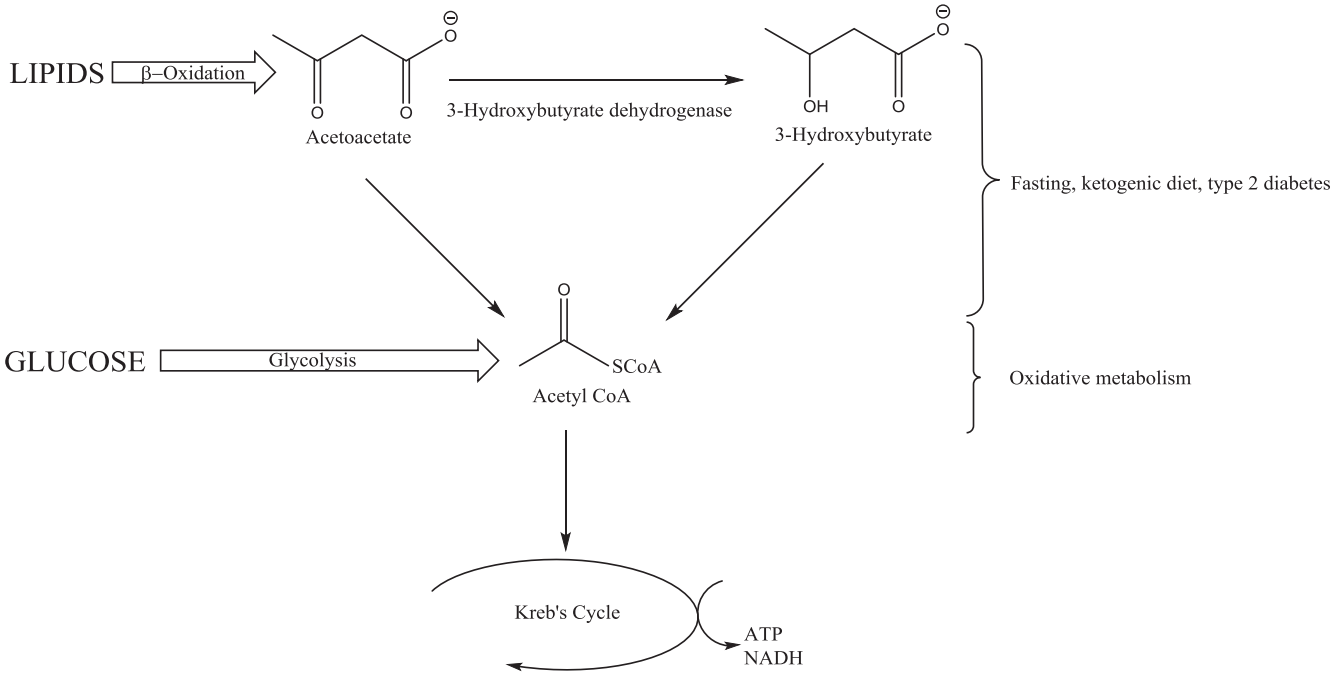

Fig. 1. Ketogenic metabolism compared with "normal" oxidative glucose metabolism. In ketogenic metabolism, during fasting and in type 2 diabetes, lipids are metabolised by β-oxidation to acetoacetate (a diketone) which is converted to 3-hydroxybutyrate (a ketone) by 3-hydroxybutyrate dehydrogenase. Both acetoacetate and 3-hydroxybutyrate can form acetyl coenzyme A (CoA) via a multistep pathway (simplified in this schematic). During normal oxidative metabolism, glucose is converted via glycolysis to acetyl coA. Acetyl coA enters Kreb's Cycle, which produces energy-rich molecules (e.g., ATP, NADH) that drive cellular metabolism. The ketogenic pathway is an ingenious way of circumventing glycolysis in times of metabolic stress.

underlying issue, carbohydrate intake could have influenced the outcomes. It is known that type 2 diabetes nearly doubles the risk for AD [1], and the similarities in the pathologies of these two diseases has led some to refer to AD as "type 3 diabetes" [16,17]. In a study showing reduced Aβ in mice fed a KD, Van der Auwera et al. [9] stated that other studies that increased fat intake without reducing carbohydrate intake resulted in the opposite effect as increased Aβ levels were observed. Finally, a therapeutic program developed by Bredeson et al. [18,19] involves a broad range of metabolic interventions, including carbohydrate intake reduction; this intervention has shown promising results in reversing early cognitive decline. These findings provide grounds for speculation that carbohydrates could play a significant role in the pathology of AD. Ultimately, the results of the study by Henderson et al. [11] indicate a need for further investigation into the role of carbohydrates in AD pathology, particularly with respect to individuals with different alleles of the *ApoE* gene.

Role of dietary carbohydrate restriction

Seneff et al. [20] have proposed a cascade effect connecting the role of the *ApoE* gene and carbohydrate intake in the development of AD (Fig. 2). This hypothesis supports the findings discussed so far.

Seneff et al. proposed that modern diets high in carbohydrates and low in fats result in excessive blood glucose levels after meals, and that this damages important proteins, including the ApoE protein. ApoE proteins are particularly susceptible to glycation, transforming them into advanced glycation end-products (AGEs). AGEs are found in large quantities in the cerebrospinal fluid and brains of individuals with AD [21]. This glycation damage to ApoE impairs its ability to transport lipids to astrocytes, ultimately leading to insufficient levels of important fats, including cholesterol, in neurons. From here, there is a cascade effect of impaired neuronal function, oxidative stress, and mitochondrial dysfunction, ultimately resulting in neuronal cell death [20].

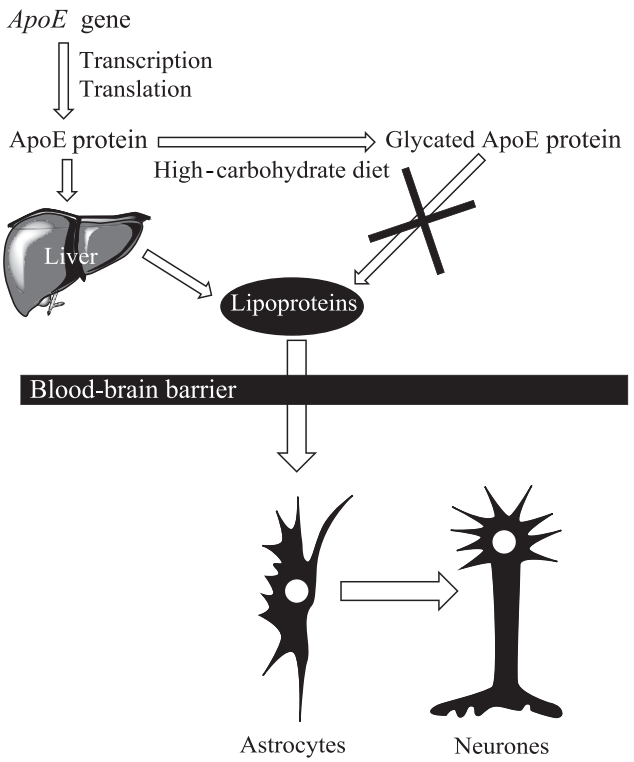

Fig. 2. Schematic representation of the link between high-carbohydrate diets and Alzheimer's disease. The *ApoE* gene is transcribed to the corresponding mRNA, which is translated to ApoE protein, which modulates lipoprotein (including cholesterol-bound protein) biosynthesis in the liver. These lipoproteins cross the blood–brain barrier and are taken up by astrocytes and transferred to neurones, where they play a key role in neuronal metabolism. High-carbohydrate diets (particularly those rich in fructose or fructose-containing carbohydrates; e.g., sucrose) inhibit the hepatic production of lipoproteins, which in turn starve neurones of these essential biochemicals, which might result in the neurodegeneration seen in Alzheimer's disease (adapted from from Seneff et al. [20]).

The cascade explanation of AD pathology [20] could underpin many of the research findings discussed here. The link between diabetes and AD, for example, could be due to insulin resistance and spikes in blood sugar increasing the glycation of ApoE proteins. Furthermore, ApoE proteins transcribed and translated from the E4 variant of the gene are three times as AGE-binding than those of other *ApoE* gene variants [22]. This suggests that *ApoE*4(+) individuals might be more susceptible to the cascade effect proposed by Seneff et al. [20], which may explain why they are more at risk for developing AD. This may also explain why Henderson et al. [11] found a significant improvement in *ApoE*4(−) but not *ApoE*4(+) individuals, as the participants in the study were still consuming carbohydrates. Finally, Aβ levels increase or decrease depending on the levels of lipidated ApoE, which means that lipidated ApoE deficits might lead to increased Aβ, whereas an abundance of lipidated ApoE likely enhances clearance of Aβ [23,24]. This could explain why Van der Auwera et al. [9] observed reduced levels of Aβ in mice that consumed a KD because the KD likely reduces glycation by lowering blood sugar levels while also increasing the availability of lipids, and both effects might lead to elevated lipidated ApoE. This increase in available lipidated ApoE also might supply astrocytes with fats that are important for neuronal growth and function, potentially preventing the cascade effect proposed by Seneff et al. [20] (Fig. 2). This accumulation of evidence suggests that glycation of the ApoE protein, and the resulting downstream effects, might explain elements of AD pathology, and a KD might alleviate damage through blood sugar stabilization and increased availability of important fats (including cholesterol).

Future research

Future research should explore the potential of a full KD as a treatment for AD, rather than focusing solely on elevating ketones via MCT, because inhibition of glycation via carbohydrate control may be an important factor in the treatment of the disease. There are four variations of the KD that could be trialed for efficacy, including the classic KD and MCTKD, the modified Atkins diet, and low-glycemic index treatment (LGIT) [14,25,26]. Each of these variations have demonstrated efficacy in treating epilepsy [13,26–28], and all could potentially be useful in the treatment of AD because they all increase KBs, and the classic KD, MCTKD, and LGIT in particular are considered low-glycemic therapies, resulting in steady glucose levels [14]. If KDs are found to demonstrate promise in treating AD, differences in efficacy between these variations could also indicate the relative importance of ketones and glycation control. The classic KD and MCTKD, for example, produce higher levels of KBs than the LGIT [14,28], so if the classic KD and MCTKD were more effective, this could indicate the importance of higher levels of KBs in treating AD. If the LGIT were just as effective, however, this may indicate that lower levels of KBs are sufficient if blood glucose is also controlled, which may indicate that glycation is a prominent factor in the development of the disease.

The potential efficacy of preventative measures also should be assessed. If the underlying cause of AD is related to lifestyle factors such as diet, with genetic factors exacerbating this in some cases, changes in modern dietary norms may reduce the prevalence of

AD in the future. Fructose, for example, produces AGEs at up to 10 times the amounts caused by glucose [29]; interestingly, fructose is present in many popular sweetened beverages and processed foods owing to the widespread use of high-fructose corn syrup by the food industry [30,31]. Sweet cravings are common in individuals with AD [32,33], and if this food preference develops early, dietary selections made by these individuals could contribute to their risk of developing the disease.

Research thus far has been limited to assessing the effects of KDs as a treatment and prevention strategy for AD. Perhaps future research should investigate how much of AD pathology is underpinned by early metabolic issues leading to ApoE glycation, and how effective early dietary interventions might be in preventing the disease. This may be important to study in individuals with genetic risk factors, major lifestyle risk factors [1], or those demonstrating early impairments in brain glucose metabolism.

Our hypothesis

We hypothesize that these dietary and metabolic influences may play a significant role in the underlying pathology of AD; therefore, a KD involving increased ketone levels and carbohydrate reduction might offer an effective treatment and prevention strategy for the disease. The elevation of KBs has the potential to improve brain metabolism, reduce accumulation of Aβ plaques, and reverse Aβ toxicity to support neurogenesis rather than neuronal cell death. Reduced carbohydrate intake might increase the achievable levels of KBs, while also contributing to the beneficial effects of the KD by preventing glycation, resulting in lower levels of AGEs, ultimately increasing the availability of lipidated ApoE. This might, in turn, prevent deficiencies of important fats, including cholesterol, in the brain, inhibiting the cascade effect proposed by Seneff et al. [20] (Fig. 2).

Conclusion

A high-fat, low-carbohydrate KD might provide an effective prevention and treatment strategy for this increasingly prevalent, debilitating neurodegenerative disease.

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