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A Novel Approach to Treating Alzheimer's Disease

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Introduction

Currently, 5.3 million Americans are living with Alzheimer's disease (AD).[1] AD is the most common cause of dementia and causes up to 50-80 percent of dementia cases according to the National Institute on Aging.[2] The disease is named after Dr. Alois Alzheimer, who first described amyloid plaques and neurofibrillary tangles. Neurofibrillary tangles begin to form in the entorhinal cortex and, along with plaque development in other areas of the brain, lead to neuronal damage, eventually causing malfunction and death of the neuron. Damage to the brain begins 10 to 20 years before onset of symptoms. The damage eventually spreads to the hippocampus, and, as the extent of damage and neuron death increases, the size of the brain decreases.

Although the cause of AD is still unclear, scientists have identified several probable causes, including genetic, environmental and lifestyle factors.[2] Familial AD is caused by mutations on certain chromosomes, which results in the formation of abnormal amyloid precursor protein (APP), the precursor for beta-amyloid. Other genetic mutations increase the amount of beta-amyloid formed, which accumulates to form plaques. Another genetic risk factor, SORL1, was discovered in 2007 and is responsible for the transportation of APP within cells. When present at low levels, the levels of beta-amyloid increase, increasing the harm to neurons. Current research on AD is focusing on the link between cognitive decline and heart disease, high blood pressure, diabetes and obesity. One theory examines decreased blood flow to the brain associated with high blood pressure and high cholesterol. This may result in decreased glucose metabolism and an increase in BACE1, the enzyme that cleaves APP, thus causing beta-amyloid deposition.[3] Scientists also are investigating lifestyle factors that may improve the outcome and progression of patients with AD. The National Institute on Aging recommends a nutritious diet, exercise, social engagement and mentally stimulating pursuits as lifestyle factors that might help reduce the risk of cognitive decline and AD.[2]

Current Treatment

Four drugs are currently indicated for the treatment of AD: donepezil (Aricept®), rivastigmine (Exelon®), galantamine (Razadyne®) and memantine (Namenda®). These drugs assist in controlling neurotransmitter release, which may decrease symptoms, but do not treat the underlying cause of AD.[2] Donepezil, rivastigmine and galantamine are acetylcholinesterase inhibitors. Inhibiting acetylcholinesterase increases the amount of acetylcholine available to neurons in the brain.[1] Acetylcholine is important for learning and memory. The disease destroys cells that synthesize and use acetylcholine. Donepezil is approved to treat all stages of the disease, whereas rivastigmine and galantamine are approved to treat mild to moderate AD. Memantine works by regulating glutamate activity and is approved for treatment of moderate to severe AD. Current treatment is aimed at maintaining cognitive function and slowing the progression of the disease. However, new research is focusing on the cause of the disease rather than treating the symptoms and progression of the disease after onset.[2]

New Approaches

In a normally functioning brain, glucose is the primary energy source, and the contribution made by fatty acids is considered small.[4] Glucose undergoes aerobic oxidation to form carbon dioxide and water. In a brain with AD, a decrease in the cerebral metabolic rate of glucose (CMR-glu) is observed early on in the process. This disturbance is known as glucose hypometabolism and has been found to occur in some patients decades before the symptoms of AD develop. Because hypometabolism occurs early and is progressive, it is a reasonable target in the treatment of AD, with a therapeutic goal of increasing the neuronal energy state. One way to reach this goal would be to maintain elevated glucose levels by using insulin sensitizers and, in some cases, insulin. However, this method is associated with significant risks, such as hypoglycemia and the lack of compliance of the patient population causing investigations into alternative energy sources.

Ketone bodies cause hyperketonemia, which can be safely induced and maintained for several hours compared to hypoglycemia. Ketone bodies readily cross the blood brain barrier and are metabolized by neurons. For decades, ketogenic diets have been used in epilepsy and Parkinson's disease as a way to decrease blood glucose levels and increase ketone bodies. These diets normally consist of 88 percent fat, 10 percent protein and 2 percent carbohydrates. When used in the management of seizures, 53.9 percent of patients had more than a 75 percent reduction in seizures one month after starting the diet. Parkinson's patients using this type of diet also showed improvement in motor scores in patients with increased ketone levels after 28 days. Although the diet showed improvements in these central nervous system diseases, it is impractical for chronic use because of the high fat intake, high number of calories and an unpalatable regimen.

Caprylidene

One of the major ketone bodies in humans is beta-hydroxybuterate (BHB). The main benefit of BHB is its conversion to acetoacetate (ACA) in the mitochondria. This generates a reducing equivalent of NADH, which increases energy in this redox couple. Conversion of ACA to acetyl-CoA then generates succinate, a substrate for complex II, which allows for possible bypass of complex I inhibition. BHB also increases acetyl-CoA levels in the mitochondria. The end result of having increased ketone levels is improvement of mitochondrial efficiency and a decrease in the number of reactive oxygen species produced. For these reasons, the new drug caprylidene, which is an orally administered medium-chain triglyceride, is being used in the treatment of hypometabolism in AD. Caprylidene is metabolized by the liver to the active ketone bodies BHB and ACA, providing an alternative energy source for the brain. Clinical trials of capylidene in patients with cognitive impair-

ments that have been completed to date have proven that elevation in plasma BHB levels with an oral dose can improve memory and attention performance in individuals with memory and cognitive impairment. Caprylidene appears to be a safe method to elevate plasma levels of ketone bodies.

Caprylidene is a medical food dispensed by prescription only that contains a formulation of medium chain triglycerides (MCTs). A medical food is defined as "a food which is formulated to be consumed or administered enterally or orally under the supervision of a physician, and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."[5] Caprylidene contains a formulation of caprylic triglyceride, which is an MCT for the clinical dietary management of the metabolic processes associated with mild to moderate AD.[6] Patients should take 40 grams (one full packet) mixed in liquid once a day after breakfast or lunch. The most common adverse effects reported by patients in clinical studies were gastrointestinal in nature. Most reported were nausea, abdominal discomfort and diarrhea.

This medical food was tested in trials that allowed subjects to remain on their prescribed medications for AD as long as they had been on a stable dose for at least three months. Most of the patients in these trials were receiving other medications for AD, including acetylcholinesterase inhibitors and/or NMDA receptor antagonists. It was determined that caprylidene can be administered as adjunctive therapy along with other AD medications. Caprylidene contains milk and soy, so it should not be used in patients that are allergic to either of these products. It also should be used with caution in patients with known hypersensitivity to palm or coconut oil and in patients at risk for ketoacidosis, such as alcoholics and uncontrolled diabetics. Also, elevated triglyceride levels were observed in patients who presented with probable metabolic syndrome; therefore, triglyceride levels should be monitored in patients with metabolic syndrome.[6]

In a double-blind, placebo-controlled clinical trial, researchers tested the hypothesis that acute elevation of serum β-hydroxybutyrate (β-OHB) levels through an oral dose of MCTs would improve memory and attention in individuals with AD or mild cognitive impairments.[7] β-OHB is a type of ketone body that appears to protect hippocampal neurons. The cognitive differences were examined between subjects with and without the APOE-ε4 allele. Missing this allele is a genetic risk factor of sporadic AD. Results demonstrated that there was an increase in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) within the ε4- group (P=0.04).

A randomized, double-blind, placebo-controlled, parallel-group study tested the hypothesis that ketosis could improve cognitive performance in AD. Clinicians administered a ketogenic compound to 152 patients with mild to moderate AD.[8] The results demonstrated that, in the population that was missing the APOE- ε4 allele, there was a significant difference in ADAS-Cog scores versus placebo on two different instances (p=0.005 and p=0.0148). It was determined that the ketogenic compound that was studied rapidly elevated serum ketone bodies in AD patients and thus resulted in significant differences in ADAS-Cog scores compared to placebo.

Patients and their caregivers should be advised that mild GI symptoms may occur with caprylidene and should be taken following a meal containing fats and proteins so that the digestion of the MCTs occurs more slowly. Sipping the drink over a period of 30 minutes can improve tolerability rather than drinking it all at once. Some patients may require starting at a lower dose (~2 tbsp) and tapering up to a full dose. Also, over-the-counter medications such as simethicone, antacids and antidiarrheals can be useful for treating GI symptoms that may occur.

Caprylidene is a novel therapeutic strategy because it treats one of the underlying causes of AD instead of treating the symptoms and progression of the disease. Because caprylidene is a safe treatment option with few side effects and no interactions with other AD medications, it can be initiated at almost any point in the treatment of AD depending on the physician's recommendations. In order for a patient to use caprylidene, they need to get a prescription from their physician and bring it into their pharmacy to be filled. Because this drug is so new, and in a relatively new class, further studies need to be conducted to prove the long-term efficacy of the medication and to solidify caprylidene's place in the treatment of AD.

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