An in Depth Investigation Behind the Neuroscience of a Ketogenic Diet's Effect on Memory and Mood

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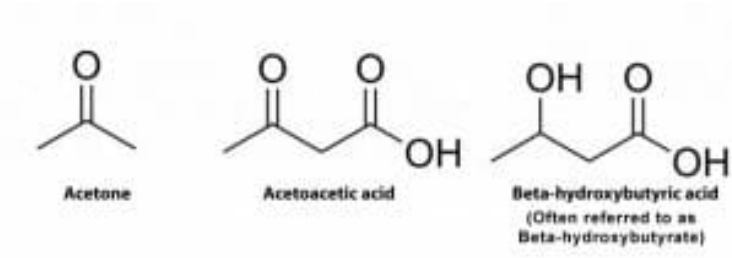
1 Background

Restrictive dieting, as a practice, has long been examined for its connection to weight-loss and disease management. Obesity is a significant health risk that increases patient susceptibility to developing type 2 diabetes, clotting disorders, and a variety of cardiovascular diseases. While improved diets have been proven to mitigate these risk factors, there remains an urgent need to identify natural tools for combating obesity. The stigmatism surrounding obesity in Western culture has dictated that dieting practices evolve to address not only health, but also a sense of confidence and fitness. However, the recent discussion of dieting has refocused on its ability to foster a more motivated, healthier and happier life, thanks to the neurological improvements directly related to dietary change, including improved sleep, focus, and memory. As a result, a novel interest has been found regarding benefits of diet and nutrition beyond weight loss. Specifically, the ketogenic diet has gained recent popularity for its profound effectiveness at enhancing mood, memory, and other cognitive functions, such as reaction time. This diet's foundation is a low-carbohydrate and high fat model that, by mimicking the process of fasting, triggers the production of ketone bodies, once the body has entered a state of prolonged ketosis (Jiang et al.). Examples of ketogenic-friendly foods include seafood such as salmon and shrimp, meat and poultry, and most types of cheese (Shoemaker and Spritzler).

Ketosis is an alternate metabolic state that occurs after the body is deprived of sufficient amounts of glucose, which are normally acquired through daily ingestion of carbohydrates. The brain normally utilizes glucose as its primary fuel source, accounting for about twenty percent of the body's glucose consumption for the formation of adenosine triphosphate (ATP), which is then utilized for energy (Mergenthaler et al.). To compensate for the lack of glucose during ketosis, fatty acids stored in the muscles, liver, and visceral fat are converted into organic compounds called ketones. Ketone bodies are an organic group consisting of a double bonded oxygen group that forms acetone, acetoacetic acid, and beta-hydroxybutyrate. These compounds are transported by medium chain triglycerides across the blood-brain barrier, which is possible due to their small ionic carbon compounds that then allow ketones to distribute throughout the brain (Jensen et al.).

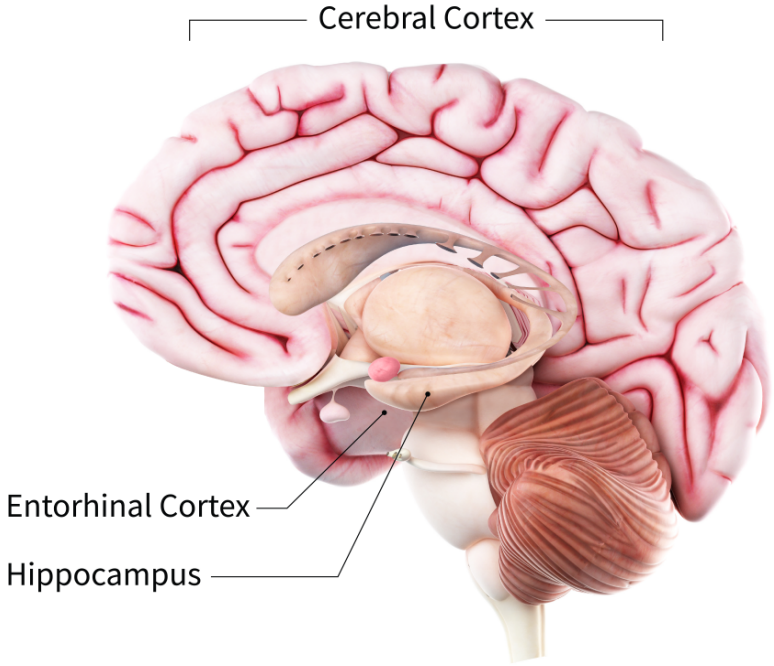
Figure 1: Chemical composition of Ketone bodies



Source: Editors, BD. "Ketone Bodies: Definition, Formation and Function." *Biology Dictionary*, 11 June 2020, https://biologydictionary.net/ketone-bodies/. Accessed 5 May. 2023.

To create ketones fatty acids are synthesized in the liver which effectively burns fat. Ketones simultaneously act as an alternative energy source for the brain to fuel physiological processes in place of glucose. This report examines how the presence of ketones circulating in the bloodstream streams as a result of the ketogenic diet can affect individual memory and mood, and the efficacy of implementing a ketogenic diet as a method of sustainable treatment to combat neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's (PD) disease.

Figure 2: Regions of the brain affected by Alzheimer's disease

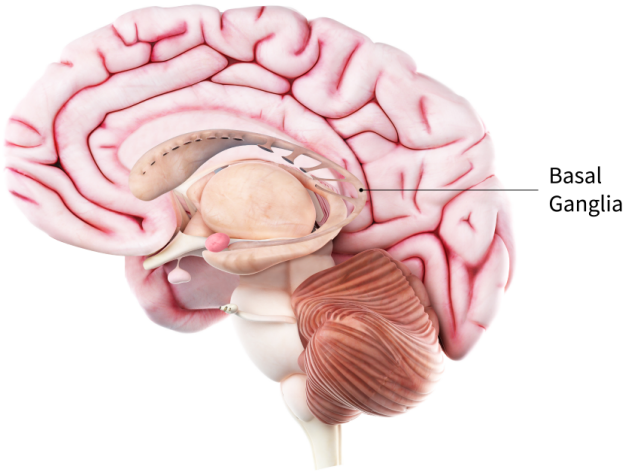


Source: "What Is Alzheimer's Disease?" *National Institute on Aging*, U.S. Department of Health and Human Services, www.nia.nih.gov/health/what-alzheimers-disease. Accessed 23 Feb. 2023.

1.1 Alzheimer's Disease

AD is a progressive brain disease that destroys neurons involved with the entorhinal cortex, hippocampus, temporal and frontal lobes. These areas depicted are interconnected forming the limbic system responsible for facilitating memory (see Figure 2). Abnormal molecular growth of proteins that accumulate in neurons associated with these areas are toxic and create Amyloid plaques and Neurofibrillary tangles that disrupt the communication between neurons leading to declining recall ability and later reasoning and behavior. The disease is most common in elderly people with age as the primary risk factor alongside diabetes patients. Increased age impedes the body's natural ability to metabolize energy substrates and even more so in AD patients: their processes that allow glucose to be metabolized become significantly disrupted (Raman). This disruption in turn disrupts brain insulin levels which is a primary regulator of "pro-inflammatory cytokines and the formation of neuroplastic and neurotrophic factors, which are essential for memory processes" (Grochowska and Przeliorz). To combat this aspect of AD, it has been theorized based on these and other findings that the presence of ketones may serve as a more effective mechanism of energy metabolism and for improved regulation of insulin transfer. Insulin transfer is crucial in AD patients who have difficulty transporting glucose in the blood to areas of the body and especially the brain that require it as a source of energy to support healthy brain function. Since it is known that AD patients suffer from glucose and nutrient deprivation in brain regions responsible for memory and cognition (e.g., the entorhinal complex and hippocampus) it is possible that mitigating this deficit by enabling delivery of necessary nutrients will improve memory function in AD patients.

Figure 3: Regions of the brain affected by Parkinson's disease



Source: "Parkinson's Disease: Causes, Symptoms, and Treatments." *National Institute on Aging*, U.S. Department of Health and Human Services, www.nia.nih.gov/health/parkinsons-disease. Accessed 23 Feb. 2023

1.2 Parkinson's Disease

PD is another progressive brain disorder that occurs when “nerve cells in the basal ganglia become impaired and/or die” (“Parkinson’s”). As depicted in Figure 3, the neurotransmitter dopamine is produced within the basal ganglia, but when these neurons are destroyed by PD, dopamine levels decline sharply. Dopamine is responsible for the feeling of pleasure by triggering the reward system in the brain. When activation of the reward system after achieving an accomplishment (e.g., satisfying a goal or consuming food) is reduced or absent, the sense of pleasure is impaired, and this impairment has been shown to progressively lead to mood and mental disorders such as depression. The absence of dopamine in PD patients poses a major issue for medical treatment as dopamine cannot be directly inserted into the brain, and medications can only act as a substitute and frequently decrease in effectiveness over prolonged use. By acting as a more efficient energy source than glucose, proper mitochondrial function can occur to provide energy to the basal ganglia and promote dopamine production (Grochowska and Przeliorz).

2 Improvements in Mental Health

A major benefit of implementing a ketogenic diet is the improvement of mood and resistance to mental illness such as depression. The reason for such improvement is the conversion of the primary ketones beta-hydroxybutyrate (BHB) into the usable resource acetoacetate to power the mitochondria by helping fuel the electron transport chain which creates a higher energy output than the conversion of glucose into pyruvate by generating more ATP (Pereira). Mitochondria are not only responsible for allocating resources to power other cells by transferring ATP energy, but they also play a key role in the release of neurotransmitters responsible for regulating feelings of stress. In response to stress, “glutamate is released from vesicles in presynaptic terminals by voltage-dependent calcium channels.” These channels are activated during a change in membrane potential as a result of depolarization which causes glutamate to “overactivate its receptors leading to a sustained influx of calcium”(Burroughs and French). To compensate for large amounts of calcium that influx during stress response, mitochondria in central nervous system neurons located in the brain and spinal cord accumulate calcium to compensate for higher levels of free cytosolic calcium (Burroughs and French). As a result, calcium levels are regulated and the body can enter resting potential and reduce stress. Additionally, they have the enzyme required for the synthesis of steroid hormones like vitamin D (Huberman and Palmer). Vitamin D is vital for neurodevelopment and mental wellness and has profound effects on increasing the development of dementia and depression when deficient. Due to its anti-inflammatory properties, the presence of toxic cerebral amyloid peptides responsible for increasing the development of dementia are reduced. Furthermore, its role in the “reduction of the buffering of increased calcium in the brain” maintains calcium levels that when in excess increase stress and lead to depression (Anjum). Mitochondria contain the vital enzyme P450scc which is responsible for catalyzing the reaction during metabolism to convert vitamin D’s hepatic 25-hydroxylation to 25 hydroxyvitamin D to be utilized throughout the body (Miller). These findings explain how when the mitochondria are disrupted many parts of the body responsible for pleasure are also

disrupted, and increased feelings of stress instead follow. Supporting research reveals a strong correlation between mental illness and mitochondria dysfunction with “Prevalence rates for depression are as high as 54% in patients with mitochondrial diseases” (Allen, et al.). Scientists speculate that this correlation occurs because of the mitochondria not transferring enough ATP energy to power neurons responsible for sending synapse signals and dopamine receptors while also failing to decrease signals from sensory neurons responsible for danger detection which heightens awareness and increases stress and anxiety. Therefore, by replacing defective mitochondria with more effective ones the body is able to trigger key neurotransmitters and reduce the activation of hormones responsible for stress response which directly correlates with decreased anxiety and depression.

3 Improvements in Cognitive Function

The presence of ketone bodies affects cognitive function which involves the ability to think, focus, learn, and remember. A few effects of a ketogenic diet is the improvements in memory, focus, and protection against cognitive decline which makes it a valuable resource for preventing neurodegenerative diseases due to the lack of medicines that establish long term protection. As previously stated, a ketogenic diet improves insulin transfer and increases ATP production in the mitochondria, both of which improve memory by stimulating the hippocampus and the entorhinal complex to become increasingly activated. An interesting discovery is that these areas of the brain become stimulated and/or rapidly revived in some cases of patients with neurodegenerative diseases who have undergone treatment with a ketogenic diet. In a study conducted with 20 non-demented elderly people (60 years or older), 11 were placed on a ketogenic diet while the others were placed on a placebo meal that replicated ketogenic foods (Ota et al.).

Figure 4: Cognitive Ability tests of a Ketogenic group versus Placebo group

At 90 Minutes	Ketogenic Meal	Placebo	P Values
Letter Number Sequencing	11.3 ± 2.2	11.3 ± 2.1	0.97
Digit Span	9.5 ± 2.7	8.6 ± 3.0	0.024
Visual Memory Span	12.2 ± 2.2	11.7 ± 3.1	0.49
At 180 Minutes			
Letter Number Sequencing	11.8 ± 1.6	11.8 ± 2.3	0.75
Digit Span	9.9 ± 2.9	9.6 ± 3.0	0.41

Visual Memory Span	12.2 ± 2.3	12.0 ± 2.0	0.64

The results revealed that the patients that underwent a ketogenic diet showed improved memory, visual attention and task switching ability indicated by the digit span test, visual memory span, and trail making test. When compared to the placebo group the ketogenic group exemplified continued improvement in the digit span and visual memory span tests even into 180 minutes in duration.

A meta review composed of many preclinical and clinical studies conducted by neurologists and psychologists reveals the more outward effects of a ketogenic diet (Jiang et al.).

Figure 5: Meta Review of outward effects that Ketogenic Diet incites

Models	Intervention	KD effects on inflammatory or other brain pathology markers	KD effects on clinical features	Study 1st author (ref)
Normal brain aging				
Animal models	KD; medium chain triglyceride	Modulates the synaptic stability and synaptic plasticity	Improves cognitive function	Newman JC [68]; Pan Y [144]; Wang D [146]
	KD	Alters expression transporters for different energy substrates and neurotransmitters	Enhances motor performance	Hernandez AR [145]
AD				
Animal models	KD; ketone ester	Reduces Aβ and hyperphosphorylated tau deposition	Relieves anxiety, improves cognitive function	Van der Auwera I [153]; Kashiwaya Y [154]
	βHB; triheptanoin	Inhibits NLRP3 inflammasome activation, microgliosis and reduces plaque formation; inhibits astrogliosis and pro-inflammatory cytokines production, improve mitochondrial status; reduces APP and increases NEP mediated by GPR109A	Improves cognitive function	Shippy DC [155]; Aso E [156]; Wu Y [157]
	Ketone ester; 3-Hydroxybutyrate methyl ester	Promotes TCA cycle metabolites and decreases mitochondrial redox potential; reduces Aβ deposition, protects mitochondrial functionality and corrects the intracellular redox state, inhibits cell apoptosis	Improves the spatial learning and working memory;	Pawlosky RJ [158]; Zhang J [159]
	βHB	Inhibits cell apoptosis with the reduction of p53, caspase-3, caspase-9, caspase-12 levels and the Bax/Bcl-2 ratio		Xie G [160]
	KD, ketone ester	Elevates the level of n-acetyl-aspartate	Improves the motor performance, does not improve cognitive performance; improves the abnormal behaviour	Brownlow ML [161]; Pawlosky RJ [162]
Human				
	Medium chain triglyceride; MMKD	Increases cerebrospinal fluid Aβ42 and decreases tau protein mediated by the alteration of gut mycobiome, gut bacteria and SCFAs, increases cerebral perfusion and cerebral KBs uptake	Improves memory in subjects with MCI	Rebello CJ [164]; Neth BJ [163]; Nagpal R [165]; Nagpal R [139]
	KD; medium chain triglyceride; MAD		Improves the quality of life and daily function; Ameliorates cognitive impairment, especially in the APOE ε4 negative patients	Phillips MCL [166]; Ota M [167]; Brandt J [168]; Henderson ST [169]; Reger MA [170]; Ohnuma T [171]
	Caprylic triglyceride		Dose not improve functional ability or cognitive impairment	Henderson ST [172]
	Medium chain triglyceride	Enhances brain ketone uptake and energy supply; enhances rCBF in specific brain regions		Croteau E [173]; Torosyan N [174]
PD				
Animal models	βHB; C8	Attenuates the loss of dopamine, improves mitochondrial respiration and ATP production, up-regulates the expression of PGC-1α and PEPCK	Improves the motor deficits	Tieu K [52]; Jonisc-Maciejak I [182]

4 Discussion

Collectively, the findings under the human model of the ketogenic diets' effect on clinical features supports that a ketogenic diet improves daily function better as focus and memory, as well as mood and diminish the negative effects of cognitive impairment in demented people like depressed mood and deranged memory.

5 Complications

Although implementing a ketogenic diet can have many benefits, it can also have negative effects on the digestive, cardiovascular, and neurological systems. Minor gastrointestinal complications such as diarrhea and constipation are common as a result of the "lack of fiber that carbohydrates provide" (Migala). Fiber provides food for key gut bacteria responsible for producing short-chain fatty acids that provide nourishment for colon cells and aid excretion, but when certain fatty acids are not sufficiently produced the colon is disrupted, leading to diarrhea and constipation. However, much larger complications can also arise such as hypoproteinemia where the body is suffering from deficient amounts of protein. Studies have revealed that hypoproteinemia occurs most commonly in people with a history of gastrointestinal pathologies that induce enteropathy such as salmonella and Crohn's disease. These findings indicate that while on a keto diet patients are more susceptible to enteropathy because of the difficulty to distribute high amounts of digested proteins, allowing for protein leakage into the small and large intestine (Newmaster et al.). Despite the increased risk for gastrointestinal complications, these only occur during the initial stages of the diet and typically span from one to four weeks. Complications can also be treated by substituting low fiber amounts with supplements and keto-friendly high fiber foods such as broccoli and artichokes while carefully monitoring the fat to carbohydrate ratio (Migala). When implementing a keto diet as a method of treatment certain ethics must be considered like the practicality of people with neurodegenerative diseases having the ability to consume keto foods. AD and PD patients have difficulty utilizing their mouth and esophagus which complicates their ability to chew and swallow normally. This is due to the blah blah. Additionally they have problems with their digestive system due to blah blah that complicates their ability to retrieve nutrients from food. These make implementing a keto diet difficult and requires subsequent methods to achieve the benefits of ketosis such as through tube feedings.

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