The Effects of Ketogenic Diets on Psychiatric Disorders Involving Mitochondrial Dysfunction: A Literature Review of the Influence of Dieting on Autism, Depression, Anxiety, and Schizophrenia

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The Effects of Ketogenic Diets on Psychiatric Disorders Involving Mitochondrial Dysfunction: A Literature Review of the Influence of Dieting on Autism, Depression, Anxiety, and Schizophrenia

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Abstract
Mitochondrial dysfunction has been linked to many psychiatric disorders. Ketogenic diets have been shown to reduce mitochondrial dysfunction and thus may be helpful to patients who suffer from these disorders. In this article, we review the effects of a ketogenic diet in patients with psychiatric disorders such as autism, depression, anxiety, and schizophrenia. Mitochondrial dysfunction, and its reversal by a ketogenic diet resulting in the relief of mental disorders, would be an excellent teaching topic on the consequences of altered cellular biology and a discussion of mitochondrial injury as one of the causes of cellular necrosis. Similarly, this information will be important in a discussion of how diet might be beneficial in the treatment of certain mental disorders. https://doi.org/10.21692/haps.2019.002

Key words: ketogenic diet, mitochondria, psychiatric conditions

Introduction
Mitochondrial phosphorylation dysfunction is associated with many psychiatric disorders including autism, depression, anxiety, and schizophrenia. A switch from a regular diet to a ketogenic diet, which induces ketosis, a high level of ketone bodies in the blood, has been shown to minimize mitochondrial dysfunction and thus may help to improve symptoms of some psychiatric disorders. There are several mechanisms by which ketogenic diets appear to improve mitochondrial dysfunction including the release of antioxidants, the reduction of inflammation, and the reduction of oxidative stress. In this article, we review the effects of a ketogenic diet in patients with specific psychiatric disorders.

Mitochondrial dysfunction, and its reversal by a ketogenic diet resulting in the relief of mental disorders, will serve as an excellent clinical exemplar in the discussion of the consequences of alterations in cellular and molecular biology, the applications of nutrition science, and topics in pathophysiology. For example, a discussion of the neurotransmitter dopamine might lead to a discussion of how Parkinson’s disease is the result of the loss of dopaminergic neurons due to mitochondrial dysfunction. The effect of mitochondrial dysfunction in psychiatric disorders, as presented here, reinforces the relationship between alterations in cellular structures and resulting abnormalities of function.

Diet is one approach to fighting obesity. Low-carbohydrate, high-fat diets, including their intense version, the ketogenic diet, have become popular dietary regimes for several reasons. Ketogenic diets have been acclaimed as an effective method to control body weight and blood glucose levels (Azar et al. 2016). Recent studies further report that this regimen has positive effects on the central nervous system (CNS) (Maalouf et al. 2009; Mattson et al. 2018). Ketogenic diets have produced beneficial effects in multiple psychiatric disorders such as autism, depression, anxiety, and schizophrenia (Evangelio et al. 2003; Herbert and Buckley 2013; Kashiwaya et al. 2013; Mantis et al. 2009; Palmer 2017; Sussman et al. 2014; Wlodarczyk et al. 2018). There could be several reasons for the reported improvements. For example, the ketogenic diet has been shown to reduce inflammation and oxidative stress (Johnson et al. 2007). The associated metabolic switch in the cellular fuel source is accompanied by cellular and molecular adaptations of neural networks in the brain that enhance their functionality and bolster their resistance to stress, injury, and disease (Mattson et al. 2018). Further understanding of the mechanism of action of the ketogenic diet suggests that ketosis, a higher than normal level of circulating ketone bodies, induced by a ketogenic diet, helps reverse the mitochondrial dysfunction commonly noted in many psychiatric disorders. This article will examine the beneficial effects of ketogenic diets on these disorders, and attempt to explain common theories as to why these positive interactions occur.

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The Role of Mitochondrial Defects in Psychiatric Disorders

Mitochondria are the most prominent source of ATP in the cell. Approximately 98% of cellular ATP is generated by these intracellular membranous structures. In addition to energy production, mitochondria are important in a variety of functions ranging from calcium buffering to regulation of apoptosis (Fattal et al. 2006).

Calcium ion concentration in the cell is critical since high levels of calcium can trigger signal transduction cascades resulting in abnormal outcomes. Mitochondria help maintain calcium homeostasis by having the ability to accumulate calcium ions in an energy dependent manner and release calcium back into the cytoplasmin. Extracellular cues resulting in the activation of the inositol triphosphate cell signaling cascade for example, increases intracellular calcium levels, which in turn increase mitochondrial calcium uptake. Greater than normal calcium uptake by the mitochondria may lead to increased metabolism and energy production or initiating apoptosis (Pinton et al. 2010; Santo-Domingo and Demaurex 2010).

In addition to calcium signaling and regulation of cell death, many chemical reactions that occur in the mitochondria result in the production of free radicals, nitric oxide, and hydrogen peroxide, which play a significant role in signaling and determining if apoptosis or proliferation is more appropriate in a given situation (Cadenas 2004). Other metabolites that are associated with the TCA cycle include acetyl coenzyme A, citrate, isocitrate, 2-oxo succinyl coenzyme A, succinate, fumarate, malate, and oxaloacetate (Frezza 2017).

The brain requires 25% of the body’s energy supply and a single neuron can consume 4.7 billion ATP molecules per second (Kramer and Bressan 2017). Given the enormous energy demand by the brain, continuous mitochondrial production of ATP may result in the buildup of harmful agents such as reactive oxygen species (ROS). Higher ROS levels are shown to trigger a positive feedback mechanism resulting in an elevated production of ROS (Zorov et al. 2014) and thus, induce mitochondrial dysfunction. Mitochondrial dysfunction can be an influential factor in the development of psychiatric disorders. In fact, several types of mitochondrial dysfunction are being linked to autism, depression, anxiety, and schizophrenia (Fattal et al. 2006; Allen et al. 2018; Griffiths and Levy 2017; Santo-Domingo and Demaurex 2010).

A major source of mitochondrial dysfunction appears to stem from the malfunctioning of the mitochondrial oxidative phosphorylation system (OXPHOS). Oxidative phosphorylation is a process of ATP production by transferring electrons from NADH or FADH2 to oxygen via a series of electron carrier proteins. Ninety percent of the ATP in the brain is produced by the OXPHOS in the mitochondria. Thus, deficiencies in this system can have devastating effects on CNS functioning (Bergman and Ben-Shachar 2016). Defects in the OXPHOS system can be attributed to either genetics or environmental factors (Rodenburg 2016). Both the psychotic symptoms in schizophrenia and autism are linked to OXPHOS dysfunction (Bergman and Ben-Shachar 2016; Griffiths and Levy 2017). Oxidative phosphorylation system dysfunction, caused by chronic mild stress, has also been seen in those suffering from depression as evidenced by decreased hypothalamus, cortex, and hippocampal neurogenesis (Allen et al. 2018). Moreover, a decrease in neurogenesis is associated with anxiety, as seen in a mouse model with Bcl-2 mutation by Einat et al. (2005).

Normal physiological processes, such as neurogenesis and the modulation of synaptic connections known as synaptic plasticity, demand large amounts of energy. Mitochondria on the dendrites and axons are responsible for calcium signaling, generating action potentials, development of new synapses, and remodeling mature synapses, all of which are integral to plasticity. During the formation of neuroplasticity, the OXPHOS must continuously produce ATP to meet high energy requirements. (Bergman and Ben-Shachar 2016).

The Ketogenic Diet and Mitochondrial Dysfunction

Due to the lack of availability of glucose associated with a ketogenic diet, the body switches to produce a large amount of ketone bodies, which in turn serve as alternate sources of energy in the metabolically active areas, such as the brain. The presence of ketone bodies, in place of glucose, appears to aid in repairing some of the damage observed in the psychiatric disorders simply by promoting mitochondrial reproduction and increasing energy production (Kramer and Bressan 2017).

Ketone bodies have also been known to possess neuroprotective properties (Cunnane et al. 2016). For example, ketogenic diets have been in clinical use for over a century as an anticonvulsive therapy. Neuroprotective qualities consist of the reduction of neuronal apoptosis and brain edema, and the production of increased levels of neurotrophins (Maalouf et al. 2009).

Though the exact mechanism of how ketogenic diets reverse some of the effects of mitochondrial dysfunction is unknown, there are several theories to explain the process, most of which are associated with the efficiency in the availability of ATP for normal neuronal function (Maalouf et al. 2009; Wlodarczyk et al. 2018). For example, ketogenic diets are thought to decrease the production of ROS and increase ATP and phosphocreatine levels, thus boosting metabolic efficiency. Another possibility is that ketogenic diets may exert a positive effect by limiting apoptosis as well as neuronal excitability (Maalouf et al. 2009). Another theory involves correction of the OXPHOS system. When there is mitochondrial damage and the OXPHOS system is not performing optimally, oxidative damage occurs to proteins, lipids, and DNA in the brain. Any
diet that has caloric restriction, which includes ketogenic diets, produces antioxidant properties and helps delay the damage caused by the oxidative effects (Maalouf et al. 2009). The final theory relates specifically to the ketogenic diet on schizophrenia in which Włodarczyk et al. (2018) hypothesize that ketogenic diets change the ratio of gamma aminobutyric acid (GABA) and glutamate in such a way that there is an increase in the synthesis of GABA as well as glutamate metabolism. Ketogenic diets seem to compensate for the disrupted GABA levels in a schizophrenic brain, leading to possible improvement of symptoms of the disease (Włodarczyk et al. 2018). Despite the gaps in our current knowledge about the exact mechanism, available evidence suggests that ketogenic diets are associated with symptomatic improvements in several psychiatric conditions.

The Ketogenic Diet and Autism

Autism is a neurodevelopmental disability that is characterized by deficits in communication and social interactions, as well as stereotypical behavior. The severity of this disability is characterized on a spectrum ranging from mild to severe. Diagnosis is determined using the Childhood Autism Rating Scale (CARS) which ranks symptoms resulting in the following scores: 15-29.5 as non-autistic, 30-36.5 as mild to moderately autistic, and 37-60 as moderate to severely autistic. The following symptoms are considered for classification: relating to people, imitation, emotional response, object use, body use, adaptation to change, visual response, listening response, taste, smell, touch response and use, fear/nervousness, verbal and nonverbal communication, activity level, and intelligent response consistency, and general impressions (Al Backer 2016).

Zarnowska et al. (2018) reported a case involving a six-year-old male with autism that revealed positive effects of a ketogenic diet. At the beginning of the study, the boy scored a 43 on the CARS, which indicates severe autism. He had trouble with emotional responses and social interactions, and he obsessively asked the same questions repeatedly. He scored an 82 on the Wechsler Intelligence Scale (WISC) IQ scale for children, which is considered borderline intellectually disabled. A ketogenic regimen was initiated at age six years and one month. Improvements became evident after one month on the diet. The boy was less aggressive and less hyperactive. After 16 months of being on the diet, another psychological evaluation was performed at age seven year and five months. This evaluation revealed a score of 27 on the CARS, which was a 16-point improvement. The improvements were listed as: less hyperactivity, fear, anxiety, emotional, and abnormal visual/auditory reactions, coupled with increased attention, improved use of objects, improved adaptability to change, and improved communication abilities. His WISC IQ tested at a 99, which is considered average (Zarnowska et al. 2018).

Similar findings were reported in another case study by Herbert and Buckley (2013). In this study, a female child started exhibiting autistic characteristics at four years of age. These included escalating tantrums, decreased eye contact, lack of social awareness or interest, and increased sensory hypersensitivities. Her language had regressed from an average four-year-old level to an 18-month level. At 11.5 years of age, the child started to experience grand mal seizures, prompting doctors to initiate a gluten/casein-free ketogenic diet at age 12. Along with improved seizure control, the child also experienced improved language and cognitive function, as well as improved social skills and increased calmness. Her initial CARS score was a 49 (severely autistic) and was reduced to a 17 (non-autistic) over the years (Herbert and Buckley 2013).

A pilot study by Evangeliou et al. (2003) involved 30 children, two were classified as mild to moderately autistic and the other 28 were classified as severely autistic. Results from this study provided additional evidence of the beneficial effects of ketogenic diets for autistic children. Eighteen of the 30 children completed six months of a ketogenic diet. Two children improved their CARS score by over 12 points. Eight children improved their score by an average of eight to twelve points. The remaining eight children achieved minor improvements of two to eight points (Evangeliou et al. 2003).

A study performed by Mantis et al. (2009) details the use of a ketogenic diet in male Mecp2(308/y) mice in reference to Rett Syndrome (RTT), an X-linked autistic spectrum neurological disorder. The disorder is characterized by impaired energy metabolism, motor impairment, social behavioral regression, and seizure susceptibility. Girls with RTT do not exhibit developmental problems until approximately 18 months of age. At this time, speech and behavioral regression become evident. Symptoms include hand wringing, anxiety, mental retardation, seizure, and other behaviors commonly associated with autism. After 30 days on a ketogenic diet, motor and sensory function was tested by grip strength, incline latency, righting reflex, visual placing, light–dark compartment, rotarod, and open field. These tests confirmed that a ketogenic diet helped improve behavioral abnormalities, specifically a reduction of anxiety when exploring a new environment. This ketogenic diet also helped prevent the onset as well as decreased severity of symptoms associated with this syndrome (Mantis et al. 2009).

The Ketogenic Diet in Depression and Anxiety

Depression is characterized by low mood, loss of interest, and decreased energy. The severity of symptoms is ranked on a spectrum from mild to severe (Sjoberg et al. 2017). Anxiety is described in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as the anticipation of a future threat and is differentiated from a real threat or fear (Crocq 2015). While some believe that pharmacologic methods are adequate to correct these conditions, research shows significant improvements from nonpharmacologic methods, including a ketogenic diet. New studies, including
Kraft and Westman (2009) examined a 70-year-old female who was diagnosed with schizophrenia at age 17 based on the presence of auditory and visual hallucinations, paranoia, and disorganized speech. She had been hospitalized multiple times with an increase in psychotic behavior despite heavy doses of antipsychotic drugs. Despite trying multiple combinations of different drugs and dosages, her schizophrenic symptoms persisted, prompting her psychiatrist to suggest nutritional intervention. After being on the ketogenic diet for eight days, she reported an absence of hallucinations and a calmer mood with no disturbances to her medication regimen. After adhering to the ketogenic diet for 12 months, the patient was still experiencing an absence of hallucinations (Kraft and Westman 2009).

Palmer (2017) describes yet another case report where a 33-year-old male had a past medical history of attention deficit hyperactivity disorder, a major depressive disorder, and schizoaffective disorder. He was put on a ketogenic diet to study the effect on the persistent positive and negative symptoms of schizophrenia. This patient had tried multiple medications such as methylphenidate, amphetamine salts, and dextroamphetamine, but symptoms persisted. The patient’s score on the Positive and Negative Symptom Scale (PANSS), which assigns a point value to the schizophrenic symptoms one experiences, was a 98 suggesting “markedly ill”. Within three weeks of a ketogenic diet, the patient reported a decrease in auditory hallucinations, improvement in mood and energy, and a better ability to concentrate. His PANSS score at this time was 49, which is considered “much improved”. A second patient described in this study, a 31-year-old female with a past medical history of major depression and schizoaffective disorder, was also put on a ketogenic diet after seeing no relief with multiple pharmacologic measures and 23 electroconvulsive therapy sessions. Before starting a ketogenic diet, her PANSS score was 107. After four weeks on a ketogenic diet, the patient reported that her delusions were no longer present, and her mood was much better. Her PANSS at this time was 70. After this trial, the patient reported that she stopped the diet and severe paranoia and persecutory delusions followed. Her medication dosage was increased, and she also resumed her ketogenic diet. However, symptoms persisted until she started fasting in order to increase ketosis. After a third day of fasting, her symptoms had resolved (Palmer 2017).

The Ketogenic Diet in Schizophrenia
Schizophrenia is a psychiatric disease that typically arises in adolescence and early adulthood. Diagnosis is associated with structural changes in the brain and abnormal dopamine transmission resulting in hallucinations and delusions (Os and Kapur 2009). A significant problem associated with schizophrenia is referred to as a P50 auditory gate, which occurs when hippocampal interneurons lack the ability to inhibit the response to auditory stimuli, leading to sensory flooding. Research, including the study performed in an analog mouse model of schizophrenia by Tregellas et al. (2015) provides hope that treatments that reduce hippocampal activity can initiate a therapeutic effect in those with schizophrenia. While on a ketogenic diet, a higher level of sensory inhibition was achieved, suggesting that this diet may have a beneficial therapeutic effect on those diagnosed with schizophrenia (Tregellas et al. 2015).

Kashiwaya et al. (2013) used a mouse model of Alzheimer’s disease to evaluate the effects of a ketogenic diet on anxiety-like symptoms. The diet was applied to a group of 15 male mice. The ketogenic diet exhibited an anxiolytic effect during Open Field Testing as evidenced by increased ambulation and exploratory behavior compared to the control group (Kashiwaya et al. 2013). Murphy et al. (2004), using a sample of 40 Wistar rats, tested a ketogenic diet in reference to depressive symptoms, or “behavioral despair”. The Porsolt test, a behavioral test, observes rat movement in water and is accepted as a reliable test for depressive symptoms in animals. This study found that during the Porsolt test, rats on a ketogenic diet spent less time immobile than those on a standard diet, meaning they were less likely to exhibit behavioral despair or depression. The results of the rats on a ketogenic diet were similar to rats that had previously been tested while on antidepressants (Murphy et al. 2004).

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A direct connection between the characteristic symptoms of the psychiatric diseases discussed here and the underlying mechanism of cellular dysfunction offers an excellent opportunity to engage students in a discussion of cell physiology and mitochondrial dysfunction.

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