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Ketogenic diet as a metabolic therapy for mood disorders: Evidence and developments

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ABSTRACT

Despite significant advances in pharmacological and non-pharmacological treatments, mood disorders remain a significant source of mental capital loss, with high rates of treatment resistance, requiring a coordinated effort in investigation and development of efficient, tolerable and accessible novel interventions. Ketogenic diet (KD) is a low-carb diet that substantially changes the energetic matrix of the body including the brain. It has been established as an effective anticonvulsant treatment, and more recently, the role of KD for mental disorders has been explored. Ketogenic diet has profound effects in multiple targets implicated in the pathophysiology of mood disorders, including but not limited to, glutamate/GABA transmission, monoamine levels, mitochondrial function and biogenesis, neurotrophism, oxidative stress, insulin dysfunction and inflammation. Preclinical studies, case reports and case series have demonstrated antidepressant and mood stabilizing effects of KD, however, to date, no clinical trials for depression or bipolar disorder have been conducted. Because of its potential pleiotropic benefits, KD should be considered as a promising intervention in research in mood disorder therapeutics, especially in treatment resistant presentations.

1. Introduction

Mood disorders are a common and prevalent group of chronic mental illnesses. In spite of significant progress in the field of biological psychiatry, mood disorders persist as a major collective challenge, with a substantial negative impact on mental capital (Kessler and Bromet, 2013). Major depressive disorder (MDD) affects 3–17% of all adults at some point in their lifetime, and bipolar disorder (BD) affects between 1 and 3% of general population (Merikangas et al., 2012; Moreira et al., 2017). Mood disorders are heterogeneous both in clinical presentation and in underpinning pathophysiology., which may account at least in part for the substantial inter-individual differences in treatment responses. Approximately one third of patients with MDD will develop clinical presentations characterized by treatment resistant depression (TRD), where patients experience a severe and more progressive clinical course, along with deleterious neurobiological changes. Although there is no consensual definition of TRD, most studies define it as insufficient symptomatic and functional improvement after two successive courses of treatment with at least two different classes of antidepressants at appropriate doses and duration (Fava, 2003). In the same way, it is estimated that about a half of individuals with BD will not be able to achieve symptomatic remission with guideline-guided treatments (Judd et al., 2003).

Recently, two major theoretical advances in the understanding of pathophysiology and clinical presentation of mood disorders had a decisive impact in the field, with promise for advancing our understanding of reasons for treatment resistance. First, the dimensional approach proposed by the Research Domain Criteria (RDoC) project, elaborated and developed by the National Institutes of Mental Health (NIMH), provided a framework for improved understanding of brain

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function (Insel et al., 2010). In its current form, the RDoC framework proposes five domains of psychopathology, which are defined using the contemporary knowledge about major brain-behavior units of expression of psychopathology. With the RDoC approach, studying the neurobiology of specific domains of depressive symptomatology such as anhedonia, rumination, suicidality, sleep disruption, appetite, among others, has become more acceptable and prioritized over conventional research methods (Heshmati and Russo, 2015; Mandell et al., 2014; Woody and Gibb, 2015)

The second advance in mood disorders was the discovery that classical presentations of recurrent MDD and BD are not only emotional and behavioral but also systemic. Obesity and metabolic syndrome are significant contributors of morbidity and mortality among patients with MDD (Woo et al., 2016; McIntyre et al., 2007). Obesity is one of the principle risk factors for cardiovascular disease and, along with dyslipidemia, hypertension and diabetes, contributes to the metabolic syndrome, which disproportionately affects more than one third of the individuals with MDD (Subramaniapillai and McIntyre, 2017). The high prevalence of metabolic abnormalities in mood disorders as well their role in pathophysiology of the disease have led to proposals that mood manifestations could be understood as an intrinsic expression of a multi-systemic syndrome, affecting the nervous, endocrine and immune systems (Mansur et al., 2015; McIntyre et al., 2007). High body weight, insulin and glucose dysregulation and inflammatory activation in this context could be proxy phenomena of cardiovascular morbidity and mortality (Czepielewski et al., 2013; McIntyre et al., 2009). Nevertheless, few studies have translated these findings in very novel metabolic therapeutic approaches to prevent or treat both psychiatric and systemic manifestations of mood disorders (Cha et al., 2017; Mansur et al., 2017).

Diet interventions present a unique and potentially useful treatment avenue for mood disorders (Wolniczak et al., 2017; Bauer et al., 2016; Sarris et al., 2015). Specifically, diets aiming at weight loss have received growing attention, including intermittent fasting (Kessler et al., 2018), Mediterranean diet (Sanchez-Villegas and Martínez-González, 2013) and caloric restriction (Zhang et al., 2015). The ketogenic diet (KD) is a high-fat, adequate-protein, low-carbohydrate diet. This diet forces the body to use fats rather than carbohydrates as the main energetic source. Normally, the carbohydrates contained in food are converted into glucose, which is the main energetic substrate for the brain. However, if there is little carbohydrate in the diet, the liver will convert fat into fatty acids and ketone bodies. The ketone bodies pass into the brain and replace glucose as an energy source. KD has been recognized as an effective therapy for treatment-resistant neuropsychiatric diseases, including epilepsy since the 1920s (Koppel and Swerdlow, 2017; Nei et al., 2014; Lefevre and Aronson, 2000; Peterman, 1924), mitochondriopathies, alternating hemiplegia of childhood (AHC), brain tumors, migraine, and autism spectrum disorder (ASD) (Verrotti et al., 2017). At least for epilepsy, KD also was reported to be associated with procognitive effects, although it is unclear to which factor this should be attributed to (i.e. the reduction of medications, improvement of depressive and anxiety symptoms) or if this is an independent effect of the diet (Garcia-Penas, 2018).

The objective of this review is to comprehensively assess the potential of KD as a novel/ innovative treatment for mood disorders, critically evaluating data from animal and human studies and discussing the potential of this dietetic intervention for research and clinical care.

2. Brain effects of ketogenic diet

The most robust data on the potential of KD in the treatment of neuropsychiatric illnesses are derived from studies with epilepsy. Case reports on KD as an intervention to control treatment-resistant seizures, especially in children, are found in the literature throughout the past century (Peterman, 1924). Several observational studies and a meta-analysis revealed that almost half of children and young people with epilepsy on this diet saw the number of seizures drop by at least half, and the effects persisted even after discontinuing the diet (Martin et al., 2016). In addition, case reports and case series suggest that KD might be effective to treat mental illnesses such as schizophrenia and mood disorders (Bostock et al., 2017).

The most recent Cochrane review in this topic identified seven randomized controlled trials with results expressed in eight publications. The authors could not conduct a meta-analysis due to the heterogeneity of the studies. Overall the results were favorable for KD, although several limitations were highlighted. These included the small sample sizes, studies only in paediatric population and attrition rates. Positive points included the relatively good tolerability, although the diet could not be palatable to be followed for a long time (Martin et al., 2016).

Regarding MDD, the potential efficacy of KD in the treatment of mood disorders was evaluated in animal models for depression. Specifically, Murphy et al. (2004) used a model developed by Porsolt et al. (1977), which is a well-established model to evaluate the antidepressant properties of new agents/substances. The model has two steps. First, the animal is placed in a container of water in which the escape is impossible. At some point, the animal stops trying to escape and becomes immobile; this part of the test is understood as “behavioral despair”. In the second part, a pretreatment with the investigational drug is administered, leading to an antidepressant effect observed through a reduction in the time spent immobile. The rats submitted to the KD group in this study spent less time immobile than did the rats in the control diet group. This suggests that the KD may have effects that are similar to antidepressant drugs (Murphy et al., 2004). Another interesting finding of this experiment was that the presence of ketosis was not required to observe a behavioral change, suggesting that perhaps the therapeutic effects of KD are not just linked its potential in induce a ketogenic state. Although the rats from the KD group had a higher level of ketosis than the control group, this level was quite low. The authors state that this finding is in line with the literature in humans with epilepsy, indicating that seizure control and behavioral changes are not always linked, while other studies on epilepsy have shown that improvements on mental status and behavior could be found even when seizure control is not achieved (MacCracken and Scalisi, 1999; Pulsifer et al., 2001; Murphy et al., 2004).

Although the mechanism by which KD acts is not fully understood, KD is clearly able to provoke reduction in frequency of seizures, indicating that KD has a direct effect in the brain (Bough and Rho, 2007; Hartman et al., 2007). Molecular, biochemical, and physiological studies tend to support the assumption that KD acts in more than one target, including changes in brain cellular energy status (Maalouf et al., 2009), reinforcement of neuroprotective and antioxidant brain defenses, as well as effects in neurotransmitters (Lima et al., 2014).

Regarding neurotransmitters, KD has been associated with changes in different monoamines, including dopamine (Dahlin et al., 2012), noradrenaline (Lima et al., 2014) and serotonin (Żarnowski et al., 2012). Dahlin et al. (2012) examined the concentrations of monoamine metabolites in cerebrospinal fluid of children with pharmacoresistant epilepsy submitted to KD for three months. They found highly significant changes before and after KD for homovanilic acid (HVA) and 5-hydroxyindole acetic acid (5-HIAA), which were both decreased during the treatment, suggesting that KD is associated with dopaminergic and serotonergic modulation. This last action was shown to be exerted through changes in kynurenine metabolism (Żarnowski et al., 2012). Nevertheless, the mechanisms involved in the regulation of metabolites of monoamines by KD remains largely unknown.

Another potential mechanism of action of KD in epilepsy is related to GABA and glutamate transmission (Lima et al., 2014; Dahlin et al., 2005). GABA is an intermediate product in the fabrication of alpha-ketoglutarate, which is synthesized in the Krebs cycle (via glutamate) and converted to GABA through the action of the enzyme glutamate

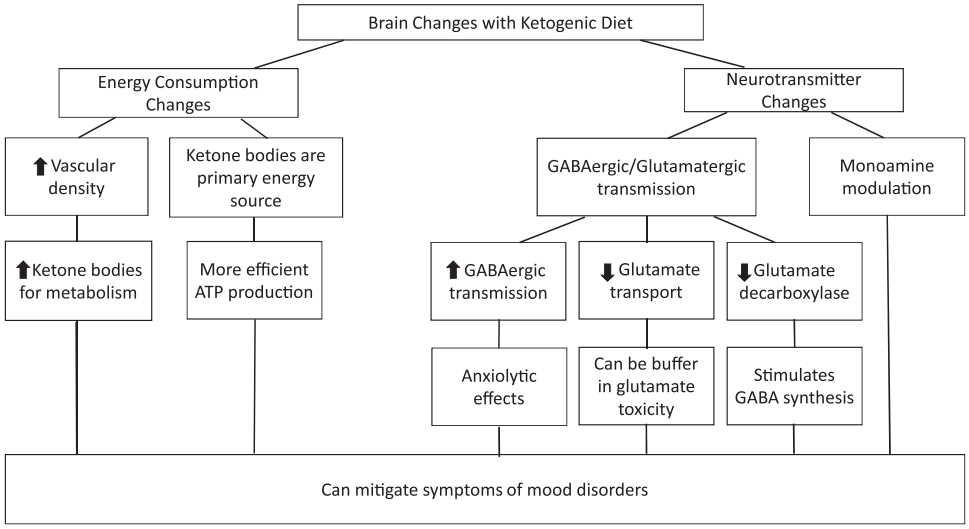

Fig. 1. Putative actions of ketogenic diet in mood disorders.

decarboxylase (McNally and Hartman, 2012). Glutamate is also altered in several mental disorders (Palomino et al., 2007). Ketogenic diet is a well-known inhibitor of glutamate decarboxylase and decreased activity of this enzyme stimulates the synthesis of GABA, thus putatively contributing to seizure control (Neal and Cross, 2010).

3. Ketogenic diet and the changes in brain energetic matrix

Interestingly, the mechanisms of action of KD seem to go far beyond the regulation of neurotransmitters (Fig. 1). Data from animal studies indicate that KD is associated with vascular brain changes, increasing vascular density at the blood-brain barrier without changes in blood flow. It has been hypothesized that increases in capillary density with increased plasma ketone bodies would increase in 40-fold the flux of ketonic bodies substrates available for brain energy metabolism (Puchowicz et al., 2007). It is plausible that this mechanism is involved in improving energetic supply to the brain during starvation. But to understand the effect of KD on energetic matrix of the brain, it is necessary to first examine the regulation of the energetic balance of this organ.

Healthy brain functioning requires the expenditure of a high amount of energy. To meet this demand, the brain tissue will consume glucose as the primary energetic substrate and will depend on mitochondrial function to convert to glucose into the usable ATP energy form. Impairments in mitochondrial function is a highly reproduced finding in mood disorders, with changes in mitochondrial morphology and number (Cataldo et al., 2010) and downregulation of mitochondrial-related genes (Iwamoto et al., 2005). It has been postulated that abnormalities in mitochondrial function could be responsible for impairments in neuroplasticity, synaptic function and changes in brain structure and function, which could be responsible for behavioral manifestations of MDD and BD. It is thought that some antidepressants and mood stabilizers, at least partially, revert these abnormalities (Villa et al., 2017).

The energetic consumption in the brain occurs through three basic components: housekeeping processes, maintenance of resting potentials and action potentials and finally, functions related to synaptic transmission (Lutas and Yellen, 2013). The housekeeping processes consume approximately 25–50% of the total brain energetic demand (Attwell and Laughlin, 2001). The maintenance of resting potentials and reversing the changes in intracellular ionic concentrations that happen after each neuronal discharge requires ATP utilization by the Na^+/K^+ pump, and by other secondary pumps such as the Ca^{2+}-ATPase, all of which requiring energy consumption (Ivannikov et al., 2010). Increases in neuronal activity are accompanied by enhancement of glycolysis in astrocytes, putatively to provide neurons with lactate as a mitochondrial fuel source (Pellerin et al., 2007). A reduction in the number and the function of astrocytes is well described in mood disorders (Nagy et al., 2015), as well as the mediators of astrocytes function, such as the reelin pathway, are reduced in postmortem hippocampuses of individuals with mood disorders, especially among those with high Body Mass Index (BMI), reinforcing the link between metabolic dysfunction and astrocytes damage in MDD and BD (Brietzke et al., 2018).

In addition, synaptic processes such as the release of neurotransmitters and neuropeptides require high amounts of energy (Attwell and Laughlin, 2001). In spite of the high demand, the capacity of the brain in storage glucose or lipids to be used as energy source is remarkably low. In addition, when the individual is under unhealthy dietary patterns, such as a Western diet, the brain tissue is almost entirely dependent on glucose as energetic source, while the periphery can utilize carbohydrates, proteins and fats. Under this condition, the astrocitary function as a critical maintainer of integrity of the blood–brain barrier (BBB) is an important mechanism involved in guaranteeing the appropriate energy supply for the brain (Gjedde et al., 2002).

As a result of a preferential energy use for the brain, several mechanisms were recognized as physiologically involved in re-routing energy to the CNS under conditions of relative or absolute energy deficiency. These mechanisms were globally named by Peters and collaborators as the “selfish brain theory” (Peters et al., 2004), which postulates that the brain prioritizes its own availability of glucose in detriment of other areas of the body. Taken together, these mechanisms would be grouped in local and systemic. On the one hand, the local actions are mediated by glutamate. When the concentration of ATP falls in the brain, an ATP-dependent potassium channel opens, allowing potassium to move to the extracellular space, thereby hyperpolarizing the neuron which becomes refractory. Excitatory (glutamatergic — high affinity for ATP) and inhibitory (GABAergic — low affinity for ATP) neurons have different sensitivity to low levels of ATP. Slightly low levels of ATP only reduce the activity of the inhibitory neurons, thus keeping the excitatory active, which in turn leads to an increased release of glutamate. In the brain, increased glutamate release promotes glucose uptake by astrocytes through the BBB. On the other hand, the systemic mechanisms will be involved in the activation of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system (SNS), which will promote increases in appetite potentially predisposing the individual to obesity (Peters et al., 2004; Mansur et al., 2013).

KD radically changes the energetic balance of the brain, which starts

to use ketone bodies as the main energetic source instead of glucose. The use of ketones by the brain involves multiple enzymatic cascades with effects that go beyond the energetic maintenance of the tissue. First, it has been postulated that ketone bodies, specifically beta-hydroxybutyrate, are more efficient in production of energy per gram of oxygen compared to glucose (Hartman et al., 2007).

In neurotransmission, there is strong evidence linking KD to regulation of glutamatergic transmission and control of glutamatergic toxicity. Indeed, this could be one of the most important mechanisms of the anti-convulsive action of this diet (Danial et al., 2013). The ketones acetoacetate and beta-hydroxybutyrate are able to inhibit the vesicular glutamate transporters, which are responsible for loading glutamate into synaptic vesicles at glutamatergic synapses (Danial et al., 2013; Juge et al., 2010). This process depends on membrane potential and requires the presence of chloride ions outside the vesicle. Ketones act by blocking the glutamate transport into synaptic vesicles by allosterically modulating the chloride dependence of the transporters. Results from animal studies suggest that this mechanism is able to act as a buffer under conditions of glutamate toxicity, such as seizures (Meldrum, 1994) and acute mood episodes (Jaso et al., 2017). Indeed, the possibility to modulate glutamatergic transmission has been considered a radical innovation in the treatment of depressive episodes (Zarate et al., 2006). In addition, it has been postulated that KD is associated to increases in GABAergic transmission, which has been implied in increases of the sensitivity to conventional anticonvulsant medications in epilepsy (Rogawski et al., 2016). Nevertheless, improvement in GABA function has very well-known anxiolytic effects, but also has been explored in the development of new antidepressants with an effect of GABA agonism, such as eszopicole (Möhler, 2012; Pehrson and Sanchez, 2015).

Regarding the effects of KD in mitochondrial function, KD seems associated to epigenetic changes in genes that are involved in mitochondrial function and also in the mitochondrial biogenesis. Further, mitochondrial dysfunction, at the level of the respiratory chain, has been extensively documented in animal model systems of depression, in post mortem brain samples obtained from individuals with mood disorder who died by suicide and by natural causes and has been a target of several clinical trials in the field (Morris et al., 2017; Bansal and Kuhad, 2016; Dean et al., 2015). Animal studies have shown that KD, specifically increased beta-hydroxybutyrate, increased the number of mitochondria and doubled the electron transport chain proteins in this organelle, thereby increasing mitochondrial biogenesis-regulating proteins in adipose tissue (Srivastava et al., 2012) and the brain (Newell et al., 2016; Bough et al., 2006).

4. Ketogenic diet as a potentially useful therapy for treatment-resistant mood disorders

A therapeutic effect of KD on mood disorders has been described in case reports involving individuals with MDD and BD, usually exhibiting characteristics of treatment resistance (Phelps et al., 2013; Bostock et al., 2017). Although currently there is no randomized clinical trial on KD for the treatment of MDD or BD, especially in the cases in which it could be more useful, such as treatment resistant presentations, several outcomes attributed to KD would be potentially beneficial:

1 Reduction of BMI and control of obesity, insulin resistance and metabolic syndrome

Obesity and metabolic syndrome are strongly correlated with treatment resistance in mood disorders (Rizvi et al., 2014). Different mechanisms have been proffered to explain this correlation, including a myriad of changes related to high BMI, such as increased inflammatory activity, alterations in the HPA axis, disturbed sleep and appetite, as well as pharmacokinetic alterations that occur with greater body fat, resulting in reduced drug bioavailability of antidepressants (Uher et al., 2009). Patients with TRD have a number of biological abnormalities. For example, they have decreased cerebral plasticity, which is proposed to be induced by low levels of brain-derived neurotrophic factor (BDNF), as well as structural and functional brain changes, including abnormalities in the dopamine- glutamate system, which are more severe in TRD than in non-TRD MDD (Romeo et al., 2018). Although TRD is frequent in clinical practice, it is less studied than other presentations of mood disorders (McIntyre et al., 2014). The well-defined effect of KD in causing weight loss in obese adults has the potential to impact metabolic and mood expression of the “metabolic-mood syndrome” (Mansur et al., 2015).

2 Prevention of accelerated and deteriorating course of mood disorders

The study of clinical trajectories of mood disorders implies mainly three groups of biological mediators: deprivation of the neurotrophin BDNF, oxidative imbalances and persistent low-grade, systemic inflammation (Moylan et al., 2013; Berk et al., 2011). Moreover, BDNF and oxidative imbalance seem to be related (Martinez-Cengotitabengoa et al., 2016). Consistent evidence supports the role of KD in the increase of BDNF (Koppel and Swerdlow, 2017), which seems to result from epigenetic mechanisms (Genzer et al., 2016). The increase of BDNF transcription due to changes in histones, at least in animals, was correlated with behavioral changes in cognitive variables, specifically spacial memory (Zhao et al., 2017). Nevertheless, other authors were not able to find the same results, and there is evidence that the increases in BDNF could be region-specific (Vizuete et al., 2013; Balietti et al., 2008). KD was also associated with antioxidant and anti-inflammatory effects. Beta-hydroxybutyrate, the ketone in which the antioxidant activity was more studied, is able to reduce the production of reactive oxygen species (ROS) thereby improving mitochondrial respiration (Pinto et al., 2017; Achanta and Rae, 2017). In addition, KD stimulates the cellular endogenous antioxidant system with the activation of nuclear factor erythroid-derived 2 (NF-E2)-related factor 2 (Nrf2), the major inducer of detoxification genes (Pinto et al., 2017). In animals, this mechanism was especially active in the hippocampus (Milder et al., 2010).

KD also has an anti-inflammatory role, becoming especially relevant for the treatment of mood disorders as a robust body of evidence has documented a permanent low-grade inflammatory status on individuals with MDD, which becomes more pronounced during acute depressive episodes (Raison, 2017; Shariq et al., 2018). Commonly used antidepressants have some anti-inflammatory activity, and the modulation of immune-inflammatory mechanisms/pathways has been the focus of several studies aiming to reduce depressive symptoms severity as well as dimensions of depressive psychopathology, such as cognition (Rosenblat et al., 2016; Grassi-Oliveira et al., 2011; Raison et al., 2013). In animals, pretreatment with KD attenuated the inflammatory response as well as the release of pro-inflammatory cytokines after stimulus with LPS (*lypopolissacaride* from *E. coli* wall) both in the blood and the brain, and also influence the arachidonic acid cascade to produce less pro-inflammatory mediators (Dupuis et al., 2015).

Even considering the remarkable potential of KD in the treatment of mood disorders, this treatment is not free of side-effects of unintended consequences, although treatment-emergent side-effects tend to minor in magnitude and transient. Relatively common side-effects are gastrointestinal complains, usually occurring in the first weeks of the implementations of KD. Hyperlipidemia is also a well-described side effect of KD (Kossoff et al., 2018). Increased serum triglycerides and total and low-density lipoprotein (LDL) cholesterol levels also have been reported, but preliminary data suggest that these alterations are usually temporary. Renal calculi historically were associated with KD, with some evidence that alkalinizing urine trough the administration of potassium citrate could reduce its incidence (Sampath et al., 2007).

In addition, in clinical practice adherence to KD could be

significantly challenging. A recent study involving a population with Alzheimer's Disease suggested that the depth and consistency of ketosis could varied a lot among subjects following KD (Taylor et al., 2017). Most data on adherence to KD are derived from children with treatment-resistant epilepsy. Considering that individuals with mood disorders could have deficits in motivation and in eating behavior as part of the symptoms of their condition, it could be anticipated that low adherence to KD could be potentially hard to achieve.

5. Future perspectives

Ketogenic diet is a safe (Arya et al., 2018; Taylor et al., 2017), relatively affordable, multi-target intervention with well-defined beneficial systemic effects, but also neurotrophic, antioxidant, neuroprotective and anti-inflammatory properties in the CNS. In the territory of drug discovery, interventions with pleiotropic actions and able to act in critical targets for illnesses trajectory are especially valuable. Ketogenic diet opens a new avenue for investigation of diet as a potential therapeutic intervention in mood disorders, offering a possibility to evaluate its effects under specific domains of psychopathology, such as anhedonia or cognition. Until now, the therapy of depression and BD primarily addressed changes few targets, most them linked to monoaminergic function aiming symptomatic control. The insufficient success of this approach combined with extensive clinical and preclinical research strongly suggest that science should move towards the functional dysregulation of brain metabolism, mitochondrial homeostasis and synaptic plasticity. The "metabolic therapy" of mood disorders should necessarily explore KD using rigorous approaches as one of the most promising interventions.

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