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Editorial Open Access

The Ketogenic Diet Approach as Metabolic Treatment for a Variety of Diseases

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Editorial

Human brain derives over 60% of its energy from ketones when glucose availability is limited. After prolonged periods of fasting or Ketogenic Diet (KD), the whole body utilizes energy obtained from Free Fatty Acids (FFAs) released from adipose tissue. However, the brain is not capable to obtain significant energy from FFAs, thus hepatic ketogenesis converts them into ketone bodies: β-Hydroxybutyrate (BHB) and acetoacetate (AcAc), while a percentage of AcAc spontaneously decarboxylates to acetone [1]. To date, it has been broadly demonstrated how the metabolic state of mild ketosis, which can be induced through KD administration, calorie restriction or fasting, represents a valid tool for the metabolic management of epilepsy and a number neurodegenerative diseases [2], Amyotrophic Lateral Sclerosis (ALS) [3], and some types of cancer [4,5]. In addition, nutritional treatments represent an effective alternative where pharmaceutical approaches fail or produce unbearable side effects and costs for public health worldwide. However, before analyzing how benefits from therapeutic ketosis could be exploited, let us mention some pivotal concepts about metabolism. Under normal conditions and mostly in western societies, a healthy brain utilizes glucose as primary energy source, which unbalance can lead to a number of neurodegenerative disorders often associated with mitochondrial impairment and glucose transport-related dysfunctions, such as in epilepsy, Traumatic Brain Injury (TBI), Parkinson's and Alzheimer's diseases [6,7]. Ketone bodies and Krebs cycle intermediates represent the best fuels for brain and other organs. In fact, through their utilization, impaired glucose metabolism may be bypassed and their neuroprotective properties may be exploited [8]. However, neuroprotective mechanisms of ketosis are currently object of studies as mechanisms of action are still not sufficiently understood. It has been shown that ketone bodies are neuroprotective as they induce a consistent increase in mitochondrial biogenesis regulating the synaptic function, and also generate ATP increases, thus reducing the reactive oxygen species production in neurological tissues [9,10], and notably inhibit superoxide synthesis in primary rat neuronal cultures exposed to hyperoxia [11]. Moreover, the main reason why the KD has been proven so effective as an anticonvulsant aFpproach is because it significantly reduces the metabolism of glucose [12]. In addition, Ma and colleagues [13] demonstrated that, at physiological concentrations, BHB and AcAc reduce spontaneous discharges of GABAergic neurons in the rat *substantia nigra*, through ATP-sensitive potassium channels. Also, a reduction of total CNS aspartate levels in association with an increase of glutamate concentrations was found during ketosis, observing a significant increase of decarboxylated glutamate to GABA, the main inhibitory neurotransmitter [14,15]. Moreover, a remarkable increase in mitochondrial transcription enzymes and proteins was observed in rat hippocampus after the administration of a KD [16]. Taken together, these findings suggest that neurons may resist to depolarization through ionic gradient and rest potential homeostasis, which explains the analogy between anticonvulsant mechanisms of orally administered ketone bodies and KD. Epilepsy represents one of the most frequent neurological pathologies as it affects about 43 million people worldwide. It results from a variety of CNS disorders and can be determined by vascular damages, genetic factors or malformations, cancers, pre-/post-natal injuries, traumatic brain injury. It has been demonstrated that the KD is one of the most effective non-pharmacological approaches in refractory epilepsy [17], although it is still unknown to and underestimated by many neurologists. Furthermore, the KD can be associated with classic antiepileptic drugs, thus significantly increasing their therapeutic results [18]. The KD induces a consistent increase in blood ketone concentration, notably AcAc and acetone [19] and it has been shown fully effective in about 50% of epileptic cases (complete seizure elimination), and partially efficient in the remaining half of patients, where it significantly improves their quality of life [20]. On another note, ketones show a neuroprotective effect also against neurodegenerative pathologies characterized by deficits in glucose metabolism, since impairment of mitochondrial function represents the main cause of a high number of neurological diseases. In fact, the following findings were published in response to ketosis: Increased cell survival and decreased seizure frequency in kainate-induced seizure models [21]; consistent reduction in lesion volume after TBI induction [22]; suppressed inflammatory cytokines and chemokines in an experimental model of multiple sclerosis [23] increase in motor neuron number in ALS transgenic models [3,24]. Notably, studies on ALS mouse models have suggested that targeting energy metabolism with metabolic therapy may prolong survival and quality of life in ALS patients. However, to date there are no clinical trials underway to test such metabolic therapies.

In addition, the KD has been shown to be effective in Alzheimer's disease (AD) models, especially since AD symptoms include seizures [25], neuronal excitability is enhanced [26,27] and mitochondrial homeostasis is altered [28]. AD progression mainly affects memory and concerns about 44 million people worldwide and this number is expected to double by 2050 (Alzheimer's Association, 2012). The main pathological hallmarks of the disease are extracellular deposits of amyloid beta, intracellular accumulation of neurofibrillary tangles (known as "tau deposition"), and progressive loss of neurons [29]. In addition, hypometabolism can be observed in several brain areas, especially in the hippocampus [30] as well as impaired mitochondrial function [31], associated with a decreased cerebral glucose utilization [32,33]. Providing ketone bodies as an alternative fuel for neurons may bypass such metabolic deficits. In order to elucidate the disease mechanism, different transgenic mouse models have been employed.

Notably, it has been shown that the KD exhibited better mitochondrial function and less oxidative stress and β-amyloid deposition when compared with normally fed controls [34]. Furthermore, KD improved rotarod performance in young (1-2 month) non-transgenic and APP +PS1 mice when fed on a KD for one month [35], while no effects on the soluble amyloid in brain or muscle could be detected by ELISA, in agreement with a previous study [36]. Additionally, it has been extensively reported that ketosis may be beneficial against cancer by decreasing blood glucose levels, the primary metabolic fuel for cancer cells [4,5]. In fact, previous work highlighted that blood ketone concentration was negatively correlated with tumor growth [37]. During the past decade, a number of researchers have been testing ways to bypass the standard/low-compliance methods to induce ketosis by developing energy intermediates to provide ketone exogenous supplementation. The main issues encountered were represented by tolerability, palatability, long term safety and costs. Notably, medium chain triglyceride oil is poorly tolerated by the gastrointestinal system. However, Dr. Henderson showed cognitive enhancement benefits from mild ketosis in tolerant subjects [6]. In addition, it has been observed that orally administered BHB and AcAc free acid forms are ineffective and pricey, whereas BHB sodium salts significantly induce a blood ketone increase in animal models [19], as well as BHB or AcAc esters, which showed a promising therapeutic potential [10,38,39]. In particular, these esters provide the advantage of generating fasting-level ketosis without any dietary restriction and were proven to be safe and well tolerated in rats [40] and humans [41]. Thus, ketone esters may represent the future "ketogenic diet in a pill" [42] paving the road to further testing. Through the past decades, confusion on physiological state of nutritional ketosis has generated some misunderstanding within the medical community [7], such as the wrong association of "therapeutic ketosis" (blood ketones comprised between 0.5 and 8 mM) with "diabetic ketoacidosis" (>10 mM). In addition, another frequent observation is that initial stages of ketosis induce a transient blood pH drop [43] due to ketone bodies accumulation in the bloodstream. However, some following works have highlighted that mild H+ load and blood pH typically return to normal ranges as long as blood ketones are maintained below 10 mM [44,45].

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