



The Broad Avenue of Therapeutic Ketosis in Neurodegenerative and Metabolism-Related Pathologies

Raffaele Pilla*

Department of Molecular Pharmacology and Physiology, External Pharmacy of Saint John of God - Fatebenefratelli Hospital, Italy

Editorial

The Ketogenic Diet (KD) represents a well-known therapeutic option for refractory epilepsy [1], although mechanisms regulating its anticonvulsant effects still remain partially unknown [2].

Human brain derives over 60% of its energy from ketones when glucose availability is limited. After prolonged periods of fasting or during a 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 [3]. Recent perspectives about the KD potentials and neuro protective properties strongly support its experimental and clinical application in a wide plethora of different neurological diseases [4]. Notably, the metabolic state of mild ketosis, induced through KD administration, calorie restriction or fasting, may be used to metabolically manage epilepsy and a number neurodegenerative syndromes [5], amyotrophic lateral sclerosis [6], and some types of cancer [7,8].

In addition, the dietary intervention could represent a useful therapeutic support in some inflammatory nervous system-related neurodegenerative pathologies, such as Parkinson's disease (PD) [9].

According to the literature, the KD might exert its neuroprotective effect through an inflammatory cytokine and chemokine modulation with a resultant reduction of lymphocyte proliferation and an oxidative stress reduction. In fact, the cytokine/chemokine modulation may prevent the activation of the inflammatory cascade with a consequent reduction in free radical production, also known as reactive oxygen species, ROS [10].

In addition, this dietary regimen has shown an intrinsic antioxidant effect, considered the experimental observation in murine models for glutathione-peroxidase increased activity in the hippocampus while following a KD [11,12]. In this light, the evident antioxidant properties of the KD may provide a significant neuroprotective effect against a number of neurodegenerative syndromes [13,14].

Moreover, the KD has shown to have protective properties on the synaptic region of hippocampal sections undergone to metabolic deficit conditions induced by low glucose levels, correlated to up-regulation of genes coding for mitochondrial ATP-synthase [15].

Similar results have been observed in a relatively recent study, where ketone bodies have shown to provide protective effects on synapses after the mitochondrial respiratory chain inhibition, through an ATP production and antioxidant activity increase [10].

Furthermore, it has been observed that the KD can lead to an augmented expression and Uncoupling Protein Activity (UCPs), which are proteins responsible for the mitochondrial transportation, which down-regulation seems to be associated to a higher susceptibility to the Experimental Autoimmune Encephalomyelitis (EAE) activity [16], thus facilitating the inflammatory processes and the ROS production, leading to worse motor performances [17].

Taken together, the experimental data suggest the adoption of KD for PD patients in order to restore the bio-energetic balance with potential neuroprotective effects [18], also due to a consistent improvement in L-Dopa absorption [19]. In fact, it has been demonstrated in some animal models that one of the major metabolites, β -hydroxybutyrate, can reduce the substantia nigra neuron loss and increase the oxygen consumption in mitochondria [20,21]. The beneficial effect of KD on

OPEN ACCESS

*Correspondence:

Raffaele Pilla, Department of Molecular Pharmacology and Physiology, External Pharmacy of Saint John of God - Fatebenefratelli Hospital, Viale Principe di Napoli 14/B, Benevento, Italy,
E-mail: raf.pilla@gmail.com

Received Date: 20 Mar 2018

Accepted Date: 20 May 2018

Published Date: 15 Jun 2018

Citation:

Pilla R. The Broad Avenue of Therapeutic Ketosis in

Neurodegenerative and Metabolism-Related Pathologies. *Ann Pharmacol Pharm.* 2018; 3(4): 1153.

Copyright © 2018 Raffaele Pilla. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

mitochondrial activity explains the improvement of patients' scores in Parkinson's disease [18]. In addition, it has been observed that cortical contusions may be decreased in an animal model of cortical injury through therapeutic ketosis [22]. Furthermore, the KD might improve the health status of patients following Traumatic Brain Injury (TBI), as this clinical condition may lead to epilepsy in some cases [23].

Overall, ketone supplements are currently being developed, and also medical foods and dietary supplements are emerging in order to help keep low blood glucose levels and elevate ketone levels without forcing any dietary restrictions on patients, whom difficult clinical conditions might make hard to follow.

Recently, an important concern that arose was that blood pH may transiently decrease during the initial phases of ketosis (Withrow, 1980). This phenomenon is due to the accumulation of ketone bodies in the bloodstream, although a few studies have proved [24-26] that the mild H⁺ load and blood pH physiologically return back to normal ranges as long as ketones are maintained below the value of 10 mM [27].

In addition, one of the hardest aspects to consider in this scenario is the common confusion about the physiological state of nutritional ketosis in the medical community: ketone bodies were previously considered as "toxic metabolites" [28], and thus usually caregivers associate the definition of "therapeutic ketosis" with "diabetic keto acidosis", which is responsible for the well-known runaway ketosis and might lead to ketone bodies concentrations of 20 mM or greater. It is pivotal to underline that the difference between the two metabolic states; in fact, ketone blood concentrations during therapeutic ketosis can vary between 0.5 mM and 8 mM [29].

References

- Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. *Lancet Neurol*. 2008;7(6):500-6.
- Rho JM, Stafstrom CE. The ketogenic diet: what has science taught us? *Epilepsy Res*. 2012;100(3):210-7.
- Cahill GF. Fuel metabolism in starvation. *Annu Rev Nutr*. 2006;26:1-22.
- Baranano KW, Hartman AL. The ketogenic diet: uses in epilepsy and other neurological illnesses. *Curr Treat Options Neurol*. 2008;10(6):410-19.
- Hartman AL, Stafstrom CE. Harnessing the power of metabolism for seizure prevention: focus on dietary treatments. *Epilepsy Behav*. 2013;26(3):266-72.
- Zhao W, Varghese M, Vempati P, Dzhun A, Cheng A, Wang J, et al. Caprylic triglyceride as a novel therapeutic approach to effectively improve the performance and attenuate the symptoms due to the motor neuron loss in ALS disease. *PLoS One*. 2012;7(11):e49191.
- Seyfried TN, Flores RE, Poff AM, D'Agostino DP. Cancer as a metabolic disease: implications for novel therapeutics. *Carcinogenesis*. 2014;35(3):515-27.
- Poff AM, Ward N, Seyfried TN, Arnold P, D'Agostino DP. Non-Toxic Metabolic Management of Metastatic Cancer in VM Mice: Novel Combination of Ketogenic Diet, Ketone Supplementation, and Hyperbaric Oxygen Therapy. *PLoS One*. 2015;10(6):e0127407.
- Paoli A, Bianco A, Damiani E, Bosco G. Ketogenic diet in neuromuscular and neurodegenerative diseases. *Biomed Res Int*. 2014;2014:474296.
- Kim DY, Vallejo J, Rho JM. Ketones prevent synaptic dysfunction induced by mitochondrial respiratory complex inhibitors. *J Neurochem*. 2010;114(1):130-41.
- Jarrett SG, Milder JB, Liang LP, Patel M. The ketogenic diet increases mitochondrial glutathione levels. *J Neurochem*. 2008;106(3):1044-51.
- Kim DY, Hao J, Liu R, Turner G, Shi FD, Rho JM. Inflammation-mediated memory dysfunction and effects of a ketogenic diet in a murine model of multiple sclerosis. *PLoS One*. 2012;7(5):e35476.
- van Horssen J, Schreibelt G, Drexhage J, Hazes T, Dijkstra CD, van der Valk P, et al. Severe oxidative damage in multiple sclerosis lesions coincides with enhanced antioxidant enzyme expression. *Free Radic Biol Med*. 2008;45(12):1729-37.
- Bo L, Dawson TM, Wesselingh S, Mork S, Choi S, Kong PA, et al. Induction of nitric oxide synthase in demyelinating regions of multiple sclerosis brains. *Ann Neurol*. 1994;36(5):778-86.
- Bough KJ, Wetherington J, Hassel B, Pare JF, Gawryluk JW, Greene JG, et al. Mitochondrial biogenesis in the anticonvulsant mechanism of the ketogenic diet. *Ann Neurol*. 2006;60(2):223-35.
- Sullivan PG, Rippey NA, Dorenbos K, Concepcion RC, Agarwal AK, Rho JM. The ketogenic diet increases mitochondrial uncoupling protein levels and activity. *Ann Neurol*. 2004;55(4):576-80.
- Vogler S, Pahnke J, Rousset S, Ricquier D, Moch H, Bruno Miroux, et al. Uncoupling protein 2 has protective function during experimental autoimmune encephalomyelitis. *Am J Pathol*. 2006;168(5):1570-5.
- Vanitallie TB, Nonas C, Di Rocco A, Boyar K, Hyams K, Heysfield SB. Treatment of Parkinson disease with diet-induced hyperketonemia: a feasibility study. *Neurology*. 2005;64(4):728-30.
- Jabre MG, Bejjani BP. Treatment of Parkinson disease with diet-induced hyperketonemia: a feasibility study. *Neurology*. 2006;66(4):617;author reply 617.
- D'Agostino DP, Pilla R, Held HE, Landon CS, Puchowicz M, Brunengraber H, et al. Therapeutic ketosis with ketone ester delays central nervous system oxygen toxicity seizures in rats. *Am J Physiol Regul Integr Comp Physiol*. 2013;304(10):R829-36.
- Viggiano A, Pilla R, Arnold P, Monda M, D'Agostino D, Coppola G, et al. Anticonvulsant properties of an oral ketone ester in a pentylentetrazole-model of seizure. *Brain Res*. 2015;1618:50-4.
- Prins ML, Fujima LS, Hovda DA. Age-dependent reduction of cortical contusion volume by ketones after traumatic brain injury. *J Neurosci Res*. 2005;82(3):413-20.
- McDougall A, Bayley M, Munce SE. The ketogenic diet as a treatment for traumatic brain injury: a scoping review. *Brain Inj*. 2018;32(4):416-22.
- Desrochers S, Dubreuil P, Brunet J, Jette M, David F, Landau BR, et al. Metabolism of (R,S)-1,3-butanediol acetoacetate esters, potential parenteral and enteral nutrients in conscious pigs. *Am J Physiol*. 1995;268(4 Pt 1):E660-7.
- Ciraolo ST, Previs SF, Fernandez CA, Agarwal KC, David F, Koshy J, et al. Model of extreme hypoglycemia in dogs made ketotic with (R,S)-1,3-butanediol acetoacetate esters. *Am J Physiol*. 1995;269(1 Pt 1):E67-75.
- Puchowicz MA, Smith CL, Bomont C, Koshy J, David F, Brunengraber H. Dog model of therapeutic ketosis induced by oral administration of R,S-1,3-butanediol diacetoacetate. *J Nutr Biochem*. 2000;11(5):281-7.
- Withrow CD. The ketogenic diet: mechanism of anticonvulsant action. *Adv Neurol*. 1980;27:635-42.
- VanItallie TB, Nufert TH. Ketones: metabolism's ugly duckling. *Nutr Rev*. 2003;61(10):327-41.
- Van der Auwera I, Wera S, Van Leuven F, Henderson ST. A ketogenic diet reduces amyloid beta 40 and 42 in a mouse model of Alzheimer's disease. *Nutr Metab (Lond)*. 2005;2:28.