Câncer cerebral. Dieta cetogênica possui grande valor

08/08/2010

Targeting energy metabolism in brain cancer with calorically restricted ketogenic diets.

Seyfried TN, Kiebish M, Mukherjee P, Marsh J. Epilepsia. 2008 Nov;49 Suppl 8:114-6.

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Information is presented on the calorically restricted ketogenic diet (CRKD) as an alternative therapy for brain cancer. In contrast to normal neurons and glia, which evolved to metabolize ketone bodies as an alternative fuel to glucose under energy-restricted conditions, brain tumor cells are largely glycolytic due to mitochondrial defects and have a reduced ability to metabolize ketone bodies. The CRKD is effective in managing brain tumor growth in animal models and in patients, and appears to act through antiangiogenic, anti-inflammatory, and proapoptotic mechanisms.
PMID: 19049606

Ketone bodies inhibit the viability of human neuroblastoma cells.

Skinner R, Trujillo A, Ma X, Beierle EA. J Pediatr Surg. 2009 Jan;44(1):212-6

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PURPOSE: Recent studies have shown that brain tumor cells, unlike normal brain cells, are largely dependent upon glucose for energy and are not able to use ketone bodies as a primary energy source. These findings are thought to be because of decreased expression of succinyl-coenzyme A:3-oxoacid coenzyme A transferase (SCOT), a key enzyme involved in ketone body metabolism. Because of their neural crest origin, we hypothesized that neuroblastoma cells would also be unable to use ketone bodies as a primary energy source. METHODS: Human foreskin fibroblasts (control) and human neuroblastoma cells (SK-N-AS) were grown in standard media with glucose (glc+), standard media without glucose (glc-), glucose-free media with acetoacetate, or glucose-free media with beta-hydroxybutyrate. Cell viability was determined with MTT [3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide] assay and apoptosis with fluorescence-activated cell sorting analysis. Immunoblotting was performed to SCOT protein. RESULTS: Neuroblastoma cell viability was significantly decreased in the acetoacetate and hydroxybutyrate media by 52% and 61%, respectively, compared with control media. In addition, neuroblastoma cells showed significantly more apoptosis in the ketone media. Viability and apoptosis in the normal fibroblasts were not affected by the culture media. The expression of SCOT protein was significantly less in human neuroblastoma cells compared with the control fibroblasts. CONCLUSIONS: Unlike human fibroblasts, neuroblastoma cells were unable to use ketone bodies as an energy source, likely because of their decreased expression of SCOT protein. Dietary manipulation using ketone bodies in accordance with SCOT expression may be a novel therapeutic strategy for neuroblastoma.
PMID: 19159745

The calorically restricted ketogenic diet, an effective alternative therapy for malignant brain cancer.

Zhou W, Mukherjee P, Kiebish MA, Markis WT, Mantis JG, Seyfried TN. Nutr Metab (Lond). 2007 Feb 21;4:5.

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BACKGROUND: Malignant brain cancer persists as a major disease of morbidity and mortality in adults and is the second leading cause of cancer death in children. Many current therapies for malignant brain tumors fail to provide long-term management because they ineffectively target tumor cells while negatively impacting the health and vitality of normal brain cells. In contrast to brain tumor cells, which lack metabolic flexibility and are largely dependent on glucose for growth and survival, normal brain cells can metabolize both glucose and ketone bodies for energy. This study evaluated the efficacy of KetoCal, a new nutritionally balanced high fat/low carbohydrate ketogenic diet for children with epilepsy, on the growth and vascularity of a malignant mouse astrocytoma (CT-2A) and a human malignant glioma (U87-MG). METHODS: Adult mice were implanted orthotopically with the malignant brain tumors and KetoCal was administered to the mice in either unrestricted amounts or in restricted amounts to reduce total caloric intake according to the manufacturers recommendation for children with refractory epilepsy. The effects KetoCal on tumor growth, vascularity, and mouse survival were compared with that of an unrestricted high carbohydrate standard diet. RESULTS: KetoCal administered in restricted amounts significantly decreased the intracerebral growth of the CT-2A and U87-MG tumors by about 65% and 35%, respectively, and significantly enhanced health and survival relative to that of the control groups receiving the standard low fat/high carbohydrate diet. The restricted KetoCal diet reduced plasma glucose levels while elevating plasma ketone body (beta-hydroxybutyrate) levels. Tumor microvessel density was less in the calorically restricted KetoCal groups than in the calorically unrestricted control groups. Moreover, gene expression for the mitochondrial enzymes, beta-hydroxybutyrate dehydrogenase and succinyl-CoA: 3-ketoacid CoA transferase, was lower in the tumors than in the contralateral normal brain suggesting that these brain tumors have reduced ability to metabolize ketone bodies for energy. CONCLUSION: The results indicate that KetoCal has anti-tumor and anti-angiogenic effects in experimental mouse and human brain tumors when administered in restricted amounts. The therapeutic effect of KetoCal for brain cancer management was due largely to the reduction of total caloric content, which reduces circulating glucose required for rapid tumor growth. A dependency on glucose for energy together with defects in ketone body metabolism largely account for why the brain tumors grow minimally on either a ketogenic-restricted diet or on a standard-restricted diet. Genes for ketone body metabolism should be useful for screening brain tumors that could be targeted with calorically restricted high fat/low carbohydrate ketogenic diets. This preclinical study indicates that restricted KetoCal is a safe and effective diet therapy and should be considered as an alternative therapeutic option for malignant brain cancer.
PMID: 17313687 [PubMed]

Diet manipulation and prevention of aging, cancer and autoimmune disease.

Jolly CA. Curr Opin Clin Nutr Metab Care. 2005 Jul;8(4):382-7.

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PURPOSE OF REVIEW: Dietary supplementation and other dietary regimens have become increasingly popular in the US population. Information regarding how different dietary constituents interact when consumed simultaneously is needed. This review examines the recent literature on how different dietary constituents may interact physiologically when consumed in combination. Furthermore, the potential human relevance of calorie restriction and nonclassical function of vitamin E is discussed. RECENT FINDINGS: Long-term calorie restriction in monkeys has shown similar beneficial effects as has been shown in rodents. Limited calorie restriction studies in humans have shown promise in reducing the incidence of heart disease and breast cancer. The combination of calorie restriction and omega-3 fatty acids may be a more potent antiinflammatory diet than either regimen alone. The type of fiber that is most protective against colon cancer may be dependent on the type of dietary fat consumed simultaneously. Vitamin E derivatives that possess no antioxidant activity may be potent inhibitors of cancer, but not normal, cell growth. SUMMARY: Dietary modification has shown its greatest beneficial effect when started prior to or immediately after the onset of disease. Also, understanding how the subtypes or isoforms of nutrients function is important since their physiological effects may be drastically different. It is important to understand the entire dietary profile of an individual when making dietary recommendations because one nutrient, or dietary ingredient, may enhance or cancel out the beneficial effects of another dietary ingredient.
PMID: 15930962

Effects of energy balance on cancer in genetically altered mice.

Patel AC, Nunez NP, Perkins SN, Barrett JC, Hursting SD. J Nutr. 2004 Dec;134(12 Suppl):3394S-3398S.

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Evidence has accumulated from laboratory-based animal experiments and population-based human epidemiological studies that lifestyle factors that affect energy balance, such as caloric intake, nutritional status, and exercise, act in concert with genetic susceptibility to influence cancer development and progression. The use of animal models with specific genetic alterations, in combination with lifestyle modifications that alter overall energy balance, has contributed to a greater understanding of the mechanistic changes occurring during carcinogenesis and to the identification of points of intervention. Studies in our laboratory focusing on the role of energy balance and genetic susceptibility in mice deficient in one (+/-) or both (-/-) alleles of the p53 tumor suppressor gene and mice with a mutant APC allele (APC(Min)) showed that calorie restriction decreases tumor burden, increases tumor latency, and decreases serum insulin-like growth factor (IGF)-1 and leptin levels. Data from our studies, combined with results from other animal and human studies, have established a role for IGF-1 in carcinogenesis. Studies using genetic models of cancer that have been interbred with mice with abnormal levels of IGF-1 will enable the examination of combined effects of energy balance and genetic alterations on the cancer process. Models that integrate lifestyle and genetic effects in a single system provide a physiologically intact system in which combination interventions and therapies for cancer prevention can be tested and validated, thus building a strong preclinical foundation that will inform the development of clinical trials and add perspective to epidemiological studies.
PMID: 15570044