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SUPPLEMENT - KETOGENIC DIET AND TREATMENTS

Targeting energy metabolism in brain cancer with calorically restricted ketogenic diets

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SUMMARY

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.

KEY WORDS: Glioma, Vascularity, Caloric restriction, Ketone bodies, Metabolic control analysis, Angiogenesis, Apoptosis, Inflammation.

BRAIN CANCER PERSISTS AS A MAJOR DISEASE OF MORTALITY AND MORBIDITY

Malignant brain cancer is a catastrophic disease of morbidity and mortality in adults and is the second leading cause of cancer death in children. Despite advances in imaging technologies, the standard therapies for malignant gliomas today are basically the same as they have been for over five decades and generally involve surgical resection followed by chemotherapy with or without radiation therapy (Seyfried & Mukherjee, 2005b). Tragically, many conventional therapies can exacerbate the disease, thus accelerating the demise of many brain cancer patients. We contend that malignant brain tumors can be managed with calorically restricted ketogenic diets (CRKD), which metabolically target tumor cells while enhancing the health and vitality of normal neurons and glia. Our contention is based on principles of evolutionary biology, metabolic control analysis, and the Warburg theory of cancer.

METABOLIC CONTROL THEORY AND BRAIN CANCER

Metabolic control analysis evaluates the degree of flux in metabolic pathways and can be used to analyze and treat complex diseases (Veech et al., 2001; Strohman, 2002; Veech, 2004). The approach is based on findings that compensatory genetic and biochemical pathways regulate the bioenergetic potential of cells and ultimately the phenotype (Greenspan, 2001; Seyfried & Mukherjee, 2005b). As rate-controlling enzymatic steps in biochemical pathways are dependent on the metabolic environment, the management of disease phenotype depends more on the flux in the entire system than on any specific metabolic step or metabolite. As abnormal energy metabolism and biological chaos characterize brain cancer, the general principles of metabolic control analysis can be employed for brain cancer management (Seyfried & Mukherjee, 2005b). This hypothesis is based on the differences in energy metabolism between normal brain cells and neoplastic cells. As long as brain tumors are provided a physiological environment conducive for their glycolytic energy needs, they will survive; when this glycolytic environment is restricted or abruptly changed, they will either growth arrest or perish (Seyfried & Mukherjee, 2005b).

Otto Warburg first elucidated the disturbance of energy metabolism as the prime cause of cancer (Warburg, 1956). This disturbance involved an irreversible injury to cellular respiration, followed by a gradual dependence on glycolysis in order to compensate for the lost energy from respiration. According to Warburg, irreversible cellular respiratory damage causes tumor cells to express aerobic glycolysis, that is, persistent glycolysis in the presence of oxygen. Aerobic glycolysis is a hallmark of most tumors including brain tumors. The switch to glycolysis is essential for maintaining viability, which requires a delta

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G′ of ATP hydrolysis of approximately –57 kJ/mol. Cells will die if this energy level is not sustained. Although the mechanisms of the Warburg theory are widely debated, our findings of mitochondrial lipid abnormalities in mouse brain tumors strongly support the theory. Moreover, structural and functional abnormalities in the mitochondria have been well documented from numerous kinds of human and mouse brain tumors (Seyfried & Mukherjee, 2005b; Arismendi-Morillo & Castellano-Ramirez, 2008; Kiebish et al., 2008). These abnormalities will restrict the ability of brain tumor cells to generate energy from ketone bodies, which bypass glycolysis and are oxidized almost exclusively in the mitochondria. Normal brain cells readily transit to ketone metabolism during therapeutic fasting or calorie restriction (Seyfried & Mukherjee, 2005b; Zhou et al., 2007). Consequently, normal neurons and glia are more adaptable to energy stress than tumor cells with defective mitochondria.

Adaptability and Variability Selection

According to Richard Potts, the evolutionary success of our species has been largely due to the inheritance of traits that bestowed adaptive versatility (Potts, 2002). These traits were honed over millions of years and enabled humans to adapt rapidly to abrupt changes in the physical environment. The adaptability to abrupt environmental change is a property of the genome that was selected for in order to ensure survival under environmental extremes. This hypothesis can be extended to the individual cells of the organism, which exist as an integrated society of cells (Sonnenschein & Soto, 1999). The success of the organism in dealing with environmental stress and disease is therefore dependent on the integrated action of all cells in the organism. Further, this integrated action depends on the flexibility of each cell's genome, which responds to both internal and external signals. Environmental forces have therefore selected those genomes that are most capable of adapting to a change to maintain homeostasis (Potts, 2002; Seyfried & Mukherjee, 2005b).

In contrast to normal cells, which readily adapt to environmental stress through integrated genetic modifications, tumor cells have impaired adaptability due to accumulated genetic abnormalities. The widely held notion that tumor cells are somehow hardy or tough and resistant to death is a gross misconception (Seyfried & Mukherjee, 2005b). How can tumor cells that express multiple mutations and mitochondrial abnormalities be more "fit" than normal cells that possess a flexible genome, normal respiratory capacity, and adaptive versatility? Accumulated genetic and epigenetic defects will reduce genomic flexibility and increase susceptibility to environmental stress, thus enhancing the likelihood of cell death. Regardless of when or how genomic defects become involved in the initiation or progression of brain tumors, these defects can be exploited for the destruction or management of the tumor according to the principles of evolutionary biology and metabolic control analysis (Seyfried & Mukherjee, 2005b). In other words, the type and the origin of genetic mutations expressed in brain tumor cells are largely irrelevant to our approach for brain tumor management. Our recent findings using calorically restricted diets, which produce energy stress, provide direct support for this hypothesis (Mukherjee et al., 2004; Seyfried & Mukherjee, 2005a; Zhou et al., 2007).

The ketogenic diet

The KD is a high-fat, low-carbohydrate diet that has been used for decades as an effective therapy for refractory seizures in children. In 1995, Nebeling and coworkers attempted the first nutritional metabolic therapy for human malignant brain cancer using a medium-chain triglyceride ketogenic diet (Nebeling et al., 1995). The objective of the study was to shift the prime substrate for energy metabolism from glucose to ketone bodies in order to disrupt tumor metabolism while maintaining the nutritional status of patients (Nebeling et al., 1995). The patients in this landmark clinical study were two young girls with nonresectable, advanced-stage brain tumors. Measurable tumor remained in both subjects following extensive radiation and chemotherapy. Although severe life-threatening adverse effects occurred from the radiation and chemotherapy, both children responded remarkably well to the KD and experienced long-term tumor management without further chemotherapy or radiation therapy. Positron emission tomography with fluorodeoxyglucose (FDG-PET) also showed a 21.8% reduction in glucose uptake at the tumor site in both subjects on the KD (Nebeling et al., 1995). These findings demonstrated that a KD, which lowered glucose and elevated ketone bodies, could reduce glycolytic energy metabolism in these brain tumors. Despite the efficacy of this therapeutic approach, together with the absence of adverse effects, no further human studies or clinical trials have been conducted on the therapeutic efficacy of the CRKD for brain cancer management in either children or adults.

We recently confirmed the findings of the Nebeling group in a series of orthotopic mouse brain tumor models treated with the CRKD and dietary energy restriction (DR) (Seyfried et al., 2003; Mukherjee et al., 2004; Zhou et al., 2007). The DR-induced inhibition of brain tumor growth is directly correlated with the reduced levels of glucose and elevated levels of ketone bodies. The gradual transition from glucose to ketone bodies as an energy source is the key for the longer term management of brain tumors. DR naturally inhibits glycolysis and tumor growth by lowering glucose levels while, at the same time, enhancing the health and vitality of normal cells and tissues through ketone body metabolism (Zhou et al., 2007). In addition to targeting energy metabolism in the tumor cells,

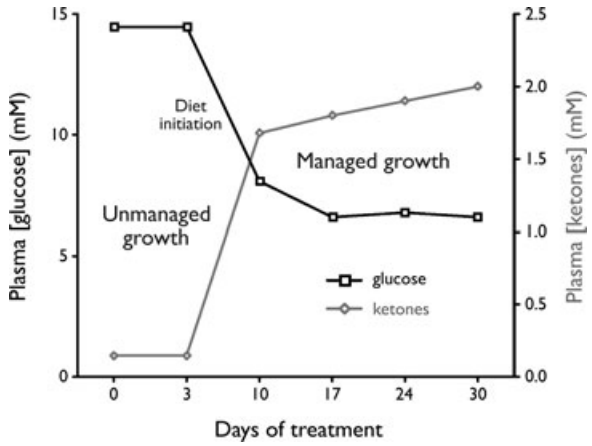

Figure 1.
Relationship of circulating glucose and ketone body levels to brain tumor management. These values are within normal physiological ranges of glucose and ketones under fasting conditions in mice and produce antiangiogenic and proapoptotic effects, causing metabolic isolation of tumor cells and delayed tumor growth. We refer to this state as the "zone of metabolic management." The glucose and ketone levels predicted for brain tumor management in human patients are 3.1–3.8 mM and 2.5–7.0 mM, respectively (Seyfried & Mukherjee, 2005b).

the CRKD can also manage tumor-associated seizures as the diet was designed originally for seizure management (Zhou et al., 2007). We also showed that DR and CRKD are powerfully antiangiogenic and proapoptotic (Mukherjee et al., 2002, 2004; Seyfried et al., 2003; Zhou et al., 2007). We suggest that brain tumor management will be better with restricted KDs than with DR alone, as circulating ketone levels are higher with restricted KD than with DR of high-carbohydrate diets. Also, the diet replaces therapeutic fasting, which is difficult for most cancer patients. Surgical debulking may also be better following the diet therapy, as the CRKD diet would slow progression and reduce angiogenesis (Zhou et al., 2007). We recently addressed issues for implementing diet therapies for managing malignant brain cancer (Seyfried & Mukherjee, 2005b; Zhou et al., 2007). The relationship of blood glucose and ketone body levels to brain tumor management is illustrated in Figure 1.

Conclusions

Our results in mice with brain tumors together with previous studies in children with malignant astrocytoma indicate that brain tumors are potentially manageable with dietary therapies that lower glucose availability and elevate ketone bodies. These diets target tumor energy metabolism and reduce tumor growth through integrated anti-inflammatory, antiangiogenic, and proapoptotic mechanisms of action. While diet therapies are not part of the current medical practice in the brain cancer field, we are hopeful that physicians and patients will come to appreciate their value in managing malignant brain tumors.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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