Role of Glucose and Ketone Bodies in the Dietary Management of Epilepsy.

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Glucose uptake into the brain is greater during epileptic seizures than during most other brain activities suggesting a key role for glucose in the initiation and spread of seizure activity. Under conditions of fasting or caloric restriction (CR), however, brain cells can also derive energy from ketone bodies (acetoacetate and beta-hydroxybutyrate). The high fat, low carbohydrate ketogenic diet (KD) was developed as an alternative to fasting for seizure management. While the mechanisms by which fasting and the KD inhibit seizures remain speculative, ketone bodies and alterations in brain energy metabolism are likely involved. The metabolism of ketones likely produces multiple changes in gene expression that lead ultimately to reduced neuronal membrane excitability and seizure management. We previously showed that caloric restriction (CR) inhibits seizure susceptibility by reducing blood glucose in the epileptic EL mouse, a model of multifactorial idiopathic epilepsy. In this study, we compared the antiepileptic efficacy of the KD with that of CR in adult EL mice. EL mice that experienced at least 15 recurrent complex partial seizures were fed either a standard (chow) diet unrestricted (SD-UR) or restricted (SD-R), and either a KD unrestricted (KD-UR) or restricted (KD-R). Each mouse served as its own control to achieve a 20% body weight reduction in the diet-restricted groups. Seizure susceptibility, body weights, and the levels of plasma glucose were measured once a week over a ten-week treatment period in each diet group. Body weights and blood glucose levels were similar over the ten-week testing period in the SD-UR and the KD-UR groups, but were significantly ($p< 0.001$) reduced in the SD-R and KD-R groups. Plasma ketone levels measured at the final week were significantly increased in the SD-R and KD-R groups compared to their respective UR groups. Seizure susceptibility remained high in both UR diet groups throughout the study. Seizure susceptibility decreased significantly ($p< 0.001$) after three weeks in both R diet groups and was managed effectively after ten weeks of diet therapy. The results indicate that seizure susceptibility is dependent on plasma glucose levels in EL mice fed either a SD or the KD and that seizure management depends more on the amount than on the origin of dietary calories. A reduction in plasma glucose levels coupled with an increase in plasma ketone levels is predicted to manage EL epileptic seizures through integrated inhibitory and excitatory neural systems.