

CAN THE KETOGENIC DIET BE ANTICONVULSANT AS WELL AS ANTIEPILEPTOGENIC?

Calorie Restriction and Ketogenic Diet Diminish Neuronal Excitability in Rat Dentate Gyrus In Vivo

Bough KJ, Schwartzkroin PA, Rho JM

Epilepsia 2003;44:752–760

PURPOSE: The ketogenic diet (KD) is an effective treatment for intractable epilepsy. However, little is known about its underlying mechanisms.

METHODS: In this study, in vivo extracellular field responses to angular bundle stimulation were recorded in the dentate gyrus of Sprague–Dawley rats fed one of three diets: ketogenic calorie-restricted (KCR), normal calorie-restricted (NCR), or normal ad libitum (NAL). Input/output curves and paired-pulse relations were used to assess network excitability. A maximal dentate activation (MDA) protocol was used to measure electrographic seizure threshold and duration.

RESULTS: Animals fed calorie-restricted (CR) diets exhibited greater paired-pulse inhibition, an elevated MDA threshold, and an absence of spreading depression-like events compared with ad libitum-fed controls. In the MDA model of epileptogenesis, the rate of increase in electrographic seizure duration after repeated stimuli was markedly reduced in KCR-fed animals compared with NCR- and NAL-fed controls.

CONCLUSIONS: These data suggest that CR, by itself, can be anticonvulsant, and treatment with a KCR diet may be both anticonvulsant and antiepileptogenic.

reduction in AED burden. However, recent laboratory efforts are beginning to provide new insights into the actions of the KD on the nervous system, and the article by Bough et al. is interesting in this regard.

The possibility that ketone bodies, such as β -hydroxybutyrate or acetoacetate, may somehow interact with neurons to augment inhibition is a plausible hypothesis. However, in a recent study, Thio et al. (1) were not able to demonstrate such an effect with in vitro electrophysiologic recordings. Bough et al. hypothesized that the glucose present in the neuronal culture medium used in the study by Thio and colleagues detracted from the “ketotic” environment and that the conditions under which the patch-clamp recordings were obtained could not be reproduced in vivo. Bough et al. undertook the present work as an in vivo study, choosing to measure evoked responses in the dentate gyrus to stimulation of perforant path of ketotic animals. In this model, they were able to demonstrate an enhancement of short-term inhibition, generally attributed to γ -aminobutyric acid (GABA) acting on GABA_A receptors, in both calorie-restricted and ketogenic calorie-restricted animals. Further, the ketogenic calorie-restricted animals also exhibited a diminution in the rate of increase in seizure duration (as measured electrographically) in the maximal dentate activation protocol, a model of epileptogenesis. This effect was not seen with calorie restriction alone. It has been proposed by Yudkoff et al. (2) that ketosis enhances conversion of glutamate to GABA, which may have relevance to the observations by Bough et al. of the antiepileptogenic effect with the ketogenic calorie-restricted diet. If ketosis is necessary to produce this effect, it is intriguing, from a mechanistic point of view, why calorie restriction alone is sufficient for protection from seizures.

COMMENTARY

The ketogenic diet (KD) remains an important alternative for children whose epilepsy is refractory to treatment with anticonvulsant medications (AEDs), especially if they are not clearly identified as candidates for epilepsy surgery. Clinicians continue to tell families that how the KD works is unknown. Epileptologists also tend to believe that improvement in the cognitive functioning of some children on the KD, as reported by their families, is reflective of improved seizure control and/or

Clinicians will be interested to know what benefits may exist in calorie restriction alone. The present work suggests that calorie restriction is sufficient for producing an anticonvulsant effect. Work by Duan and colleagues (3,4) at the National Institute on Aging has focused on the role of dietary restriction on neurotrophins, specifically, brain-derived neurotrophic factor, and its neuroprotective properties. Such neuroprotection potentially could be related to an antiepileptogenic effect. The mechanism of neuroprotective action of neurotrophins may comprise defense against oxidative damage, including

free-radical–induced neuronal injury. Although protection from oxidative injury may be mediated by the neurotrophins in the calorie restriction–alone diet, other mechanisms can come into play with ketosis. The relation of the KD to neuroprotection could be related to its recently demonstrated ability to increase the expression of mitochondrial uncoupling proteins and to reduce the production of reactive oxygen species (5).

Wu et al. (6) demonstrated that saturated fats may have a negative effect on brain-derived neurotrophic factor levels. The popular form of KD, as followed in the United States, uses saturated fats extensively. An abstract, recently presented at the Annual Meeting of the American Epilepsy Society, reported an anticonvulsant effect from the Atkins diet (7), which also liberally uses saturated fats. Experiments could be undertaken to incorporate these variations in the *type* of fat (e.g., saturated vs. unsaturated, monounsaturated vs. polyunsaturated, or ω -3 fatty acids) to see if it has major effects on disease modification in epilepsy in addition to the anticonvulsant effects—a topic of substantial interest to all clinicians.

by Raman Sankar, M.D., Ph.D.

References

1. Thio LL, Wong M, Yamada KA. Ketone bodies do not directly alter excitatory or inhibitory hippocampal synaptic transmission. *Neurology* 2000;54:325–331.
2. Yudkoff M, Daikhin Y, Nissim I, Lazarow A, Nissim I. Ketogenic diet, amino acid metabolism, and seizure control. *J Neurosci Res* 2001;66:931–940.
3. Duan W, Lee J, Guo Z, Mattson MP. Dietary restriction stimulates BDNF production in the brain and thereby protects neurons against excitotoxic injury. *J Mol Neurosci* 2001;16:1–12.
4. Duan W, Guo Z, Jiang H, Ware M, Li XJ, Mattson MP. Dietary restriction normalizes glucose metabolism and BDNF levels, slows disease progression, and increases survival in Huntington mutant mice. *Proc Natl Acad Sci U S A* 2003;100:2911–2916.
5. Sullivan PG, Rippey NA, Rho JM. A ketogenic diet increases the expression of mitochondrial uncoupling proteins UCP2, UCP4 and UCP5/BMCP1 in mouse hippocampus. *Epilepsia* 2003;44:283.
6. Wu A, Molteni R, Ying Z, Gomez-Pinilla F. A saturated-fat diet aggravates the outcome of traumatic brain injury on hippocampal plasticity and cognitive function by reducing brain-derived neurotrophic factor. *Neuroscience* 2003;119:365–375.
7. Kossoff EH, Krauss GL, McGrogan JR, Freeman JM. Efficacy of the Atkins diet as therapy for intractable epilepsy. *Neurology* 2003;61:1789–1791.