

## HOW DOES THE KETOGENIC DIET WORK?

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

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**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.

that was restricted in quantity to match the caloric content of the ketogenic diet. As expected, ketonemia (measured by plasma levels of  $\beta$ -hydroxybutyrate) was marked in rats on the ketogenic diet compared with both control groups. Field potentials recorded *in vivo* from the dentate gyrus granule cells demonstrated numerous alterations in rats fed the ketogenic diet. These alterations included decreases in population-spike amplitude, which appeared to be mediated by decreases in evoked field excitatory postsynaptic potentials (fEPSPs). An increase in short-latency paired-pulse inhibition was noted, suggesting enhanced  $\gamma$ -aminobutyric acid (GABA)<sub>A</sub> receptor-mediated synaptic transmission. Electrographic seizure susceptibility, as measured by the threshold for maximal dentate activation, also was decreased. These changes are all consistent with the suggestion that the ketogenic diet decreases synaptic excitation and enhances synaptic inhibition and that these fundamental alterations in synaptic physiology could be responsible for the anticonvulsant actions of the diet.

What was surprising from the study is that caloric restriction was equally effective in altering each of these measures of synaptic and network excitability. Because only a mild degree of ketonemia was observed in the calorie-restricted diet group, one must wonder whether ketosis is responsible for the anticonvulsant actions of the ketogenic diet, or is fasting sufficient to limit seizure generation—at least in dentate granule cells. One experimental outcome that was altered in the ketogenic diet group and not in calorie-restricted controls was an increase in electrographic seizure duration with repeated electrical stimulation. Seizure duration increased in both control groups but much less so in rats on the ketogenic diet. This suggests that processes of epileptogenesis may be particularly sensitive to ketosis.

This study provides a useful model to evaluate the effects of calorie restriction and the ketogenic diet. Moreover, it provides important new mechanistic insights into the ways these diets may control seizure susceptibility and epileptogenesis. Some obvious follow-up experiments would be to record from individual granule cells of *in vitro* slices taken from treated animals. However, as the authors point out, conducting such recordings requires perfusing slices with an artificial cerebrospinal fluid that contains high levels of glucose. This would be problematic because the glucose could quickly eliminate the effects of the both calorie restriction and ketosis. Thus one is relegated to *in vivo* recordings that are more difficult and far less amenable

## COMMENTARY

**P** Previous experimental studies in animal models have documented that a ketogenic diet is able to decrease susceptibility to seizures and retard the process of epileptogenesis. However, the cellular and molecular events responsible for either suppression of seizures or epileptogenesis are unknown. The study by Bough et al. addresses these issues in normal rats (38 days old) that were placed on a ketogenic diet for 1 month. Control rats received either a normal diet or a normal calorie-restricted diet. The rats in the latter group received normal food

to experimental manipulation. In this regard, the experimental and technical challenges of creating relevant animal models have recently been thoroughly discussed (1). Included in this analysis are the difficulties of conducting similar studies in developing animals. Because the ketogenic diet is especially effective and most widely used in children, the experimental use of immature animals would be highly desirable. However, the ketogenic diet cannot be initiated until after mouse pups are weaned. Moreover, from a neurodevelopmental standpoint, placing a mouse on a diet for 3 weeks would be equivalent to many years of treatment in a human. The biological impact of a treatment that extends across innumerable critical stages in the molecular maturation of the brain, as opposed to a restricted window

in time, is likely to be substantial. Nonetheless, experiments in more mature animals, like those reviewed here, are practical and will give much-needed insights into how the ketogenic diet may work, providing the hope that more easily managed and effective therapies may be developed for intractable seizure disorders.

*by John W. Swann, Ph.D.*

## Reference

1. Rho JM, Kim DW, Robbins CA, Anderson GD, Schwartzkroin PA. Age-dependent differences in flurothyl seizure sensitivity in mice treated with a ketogenic diet. *Epilepsy Res* 1999;37:233–240.