KOPF CARRIER

November 2016

Kopf Carrier #89

PUBLISHED BY DAVID KOPF INSTRUMENTS ■ TUJUNGA, CALIFORNIA

# Neuroscience Reviews: Treating Epilepsy with Ketogenic Diets

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## Introduction

Epilepsy is a neural circuit disorder affecting more than 70 million people worldwide. In general, spontaneous seizures are characterized by bursts of excessive neural activity that can take on a variety of forms, patterns and severities. Although mechanisms controlling brain excitability are thought to be the cause in most forms of epileptiform activity (Armijo et al., 2005), there is now considerable evidence that non-excitable elements of the brain, such as astrocytes, the microvasculature and the immune system also contribute to seizure onset (Bough and Rho, 2007; Carmignoto and Haydon, 2012; Bien and Bauer, 2014). Current antiseizure drugs provide symptomatic relief (i.e., suppress seizures) for most patients, but do not have the ability to eradicate or reverse epileptiform activity. In this regard, approximately 30% of patients with intractable epilepsy fail to respond to clinically available drugs often because poorly tolerated side-effects limit adequate dosing. Thus, there is a pressing need for developing alternative therapies for drug-resistant epilepsy. In this brief review, I discuss the use of a ketogenic diet which is a high-fat, low-carbohydrate and adequate protein diet that seems to be an effective (non-pharmacological) treatment for intractable epilepsy (Hartman et al., 2007).

## Pharmacology of Antiseizure Drugs

Antiseizure drugs generally act on several molecular targets, including ligand- and voltage-gated ion channels (e.g., potassium Kv4.2 and Kv7; sodium Nav1.1 and Nav1) that regulate the initiation and propagation of action potentials along the nodes of Ranvier (Catterall et al., 2010; Lerche et al., 2013). These voltage-gated ion channels mediate hyperpolarizing A- (and M)-type currents in the brain and thus exert considerable control over the excitability of neurons (Abdelsayed and Sokolov, 2013). Accordingly, antiseizure drugs such as ezogabine and perampanel act by modulating voltage-gated ion channels; other drugs (e.g., clobazam) act by enhancing γ-aminobutyric acid (GABA)-mediated inhibition through effects on GABAA receptors, the GABA transporter 1, the GABA uptake transporter or GABA transaminase (a ubiquitous enzyme that metabolizes GABA; Avoli and de Curtis, 2011). The end-result of this intricate pharmacology is that neurons show a significant reduction in action potential streams, a basic process of nerve cell communication. It should be noted that patients with poorly controlled epilepsy have a higher risk for sudden unexplained death in epilepsy or SUDEP (Asadi-Pooya and Sperling, 2005), perhaps due to a mutation of the gene for potassium

Kv1.1 which is also required for proper heart function (Eastaugh et al., 2015). With approximately one third of people with epilepsy not achieving adequate seizure control, there is a critical need to identify alternative therapies that reduce risk factors for SUDEP and spontaneous seizures in general.

## Temporal Lobe Epilepsy with Hippocampal Sclerosis

Seizure and epileptic activity are considered either to originate and evolve in unilateral cell networks, or to rapidly encompass both cerebral hemispheres. One type of epilepsy is temporal lobe epilepsy with hippocampal sclerosis which is often caused by status epilepticus or seizure clusters (Armstrong, 2005; Abend et al., 2014). The human hippocampus consists of several functionally and histologically different subfields known to be differentially affected in temporal lobe epilepsy (Fig. 1). The hippocampus along with the amygdala appears to contribute to the generation and propagation of epileptiform phenomena in temporal lobe epilepsy. For example, ictal symptoms such as dreamy states (e.g., déjà vu, memory flashbacks and transitory hallucinations), epigastric auras and/or sympathetic outflow with cardiovascular changes are often linked to seizure foci in the hippocampus and amygdala (Bozzi et al., 2012). Thus, the hippocampal formation is recognized to be a primary epileptogenic zone. Identifying features of the epileptogenic zone that predispose certain individuals to aberrant circuit activity is an important experimental aim for reducing not only status epilepticus but also levels of chronic cognitive and behavioral comorbidity.

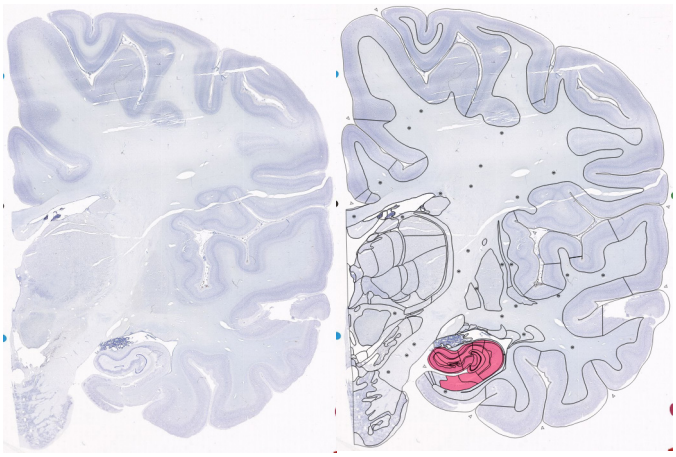

Fig. 1. The human hippocampus is an epileptogenic zone. As in most epileptic conditions, temporal lobe epilepsy with hippocampal sclerosis can be difficult to control with clinically available antiseizure drugs. In addition, surgical intervention often fails to achieve seizure-free results in patients with temporal lobe epilepsy. Given that epilepsy is a neural circuit disorder, the possibility that erratic neural excitation can be treated with a ketogenic diet suggests that energy metabolism between neurons and astrocytes is a potential drug target (Sada et al., 2015). The hippocampus (Nissl stain, red color) is part of the limbic network (i.e., brain's medial temporal lobe). The hippocampus is involved in the storage of long-term memory traces. Scale bar = 12449 µm. Image credit: Allen Institute.

## A Ketogenic Diet Suppresses Seizures

The brain does not store energy as glycogen or fats as other organs do. In fact, brain neurons are unable to metabolize fatty acids for energy. Instead, neurons rely entirely on glucose to meet molecular, metabolic and physiological demands typical of long-lived species. As an alternative to glucose consumption, neurons can draw energy from ketones such as acetoacetate and β-hydroxybutyrate which are released from liver hepatocytes in response to intermittent dietary energy restriction or fasting (Mattson et al., 2014; Fig. 2). Remarkably, a metabolic shift to ketogenesis appears to dramatically reduce seizures, particularly in patients with drug-resistant epilepsy (Kossoff, 2004). Although developed in 1921, many neurologists are not familiar with the so-called ketogenic diet as an alternative therapeutic approach for treating seizures and epileptiform activity. Regardless, the shift to ketogenesis appears to indirectly regulate neural excitability via 5'-triphosphate (ATP)-sensitive potassium channels (KATP channels) and vesicular glutamate receptors (Hartman et al., 2011). As indicated above, ligand- and voltage-gated

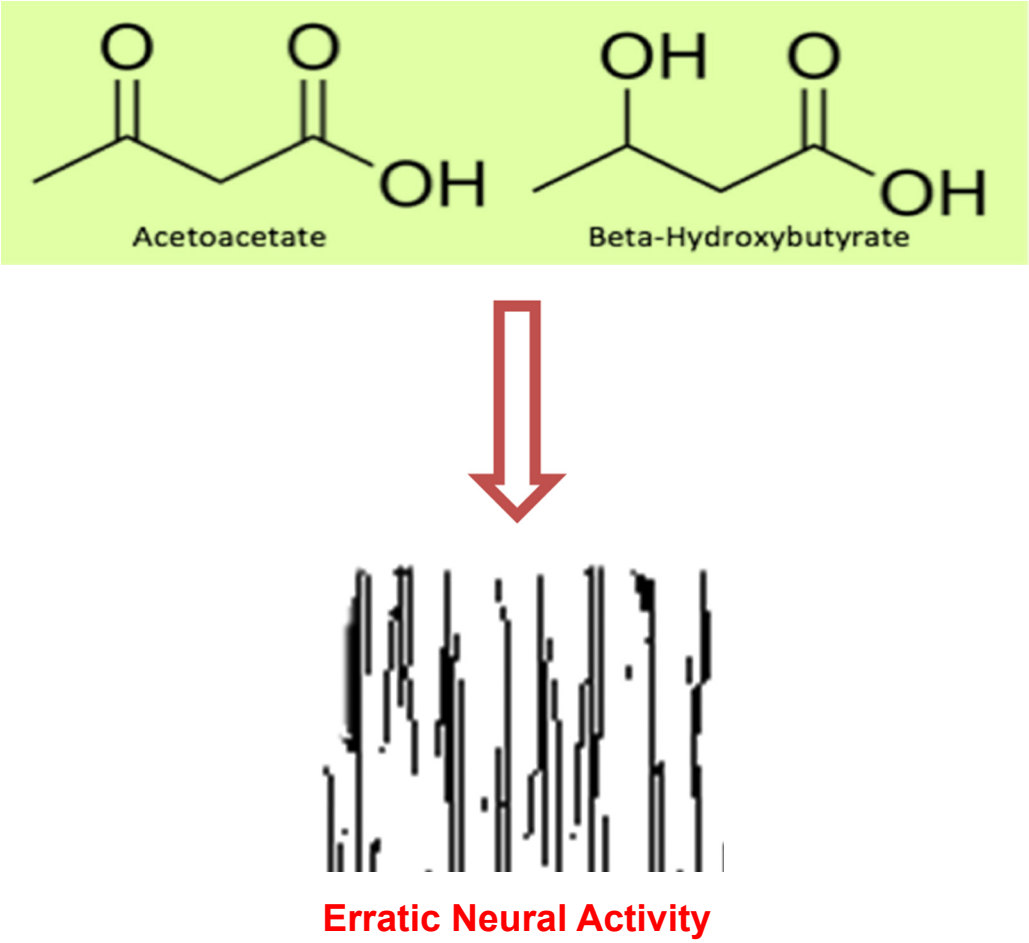


Fig. 2. Epileptic seizures (as detected by electroencephalogram recordings) have different causes, including brain malformations, intracranial hemorrhage and in children, fever (febrile seizures). The so-called ketogenic diet is a modifying therapeutic strategy for patients with epilepsy. Ketones such as β-hydroxybutyrate are organic compounds that contain a carbonyl group (a carbon-oxygen double bond). Ketones are derived from hepatocytes when liver glycogen stores become depleted within 10-12 hours of fasting (Mattson et al., 2014). Several intermediate biochemical steps occur before ketones are released into the blood where they are transported to the brain, where they are taken up by all nerve cells. Ketone molecules appear to have beneficial effects on cells with a high energy demand (e.g., neurons).

ion channels and membrane-bound receptors are intricately involved in generating electrical currents within and between neural circuits. Interestingly, ketone levels and activation of SIRT1, a nutrient-responsive signaling pathway, also appear to attenuate the progression of Alzheimer's disease and other age-related disorders (Hertz et al., 2015; Constant et al., 2012). Thus, it is clear that dietary interventions in the form of circulating ketones or caloric-restriction regimens may be relatively easy ways to mitigate excessive and erratic neural activity in the brain (Sada et al., 2015). Further studies are required to better elucidate the molecular and cellular mechanisms by which ketone-based diets affect health and disease susceptibility.

## Conclusions

Epilepsy shows a remarkable clinical heterogeneity. Antiseizure drugs have a number of mechanisms of action that target brain excitability networks. The potentiation of GABA inhibitory neurotransmission represents a well-known antiseizure effect. The ketogenic diet where > 80% of calories is derived from fat is an effective treatment for epilepsy. Drugs that block energy metabolism in both neurons and astrocytes (the other major cell type of the brain) can potentially be used to treat epilepsy (Sada et al., 2015).

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## Biography

Dr. German Torres received a Ph.D. from the University of California at Santa Barbara and is currently an Associate Professor in the Department of Biomedical Sciences at the New York Institute of Technology, College of Osteopathic Medicine. His specific research interests are centered on the biological basis of brain disorders.

## Editor's Column

It is time once again for the Big Meeting: The Society for Neuroscience meeting. This year is in one of my favorite cities, San Diego, from November 12-16. Please stop by the David Kopf Instruments booth, number 2031, to say hi to the Kopf crew and look at the great array of stereotaxic instruments and related equipment that will be on display. Carol Kopf (President of Kopf Instruments) will be there, as will Dawn Gelsinger who many of you know, so be sure to say hi to them. David Kopf Instruments presents the most complete and durable line of stereotaxic instruments in the world. Also, David Kopf Instruments has sponsored the *Kopf Carrier* for 43 years (the first issue was in 1973) as a service to the neuroscience community.

In addition to the booth, David Kopf Instruments sponsors the David Kopf Lecture on Neuroethics. That lecture will be given by Thomas Albright, Ph.D. from the Salk Institute and will be on Monday, November 14 from 10:00-11:10 am. The title of the lecture is "Reforming Forensic Science: Some Insights from Research on Vision and Memory". This will be a very interesting and informative lecture, so do plan to attend.

There is another quite interesting meeting being held just prior to the SFN meeting; the International Neuroethics Society meeting. It will occur on November 10-11 in San Diego. The INS is an organization devoted to furthering the study and integration of ethical issues in the field of neuroscience. The membership of the organization is international and expanding. You should consider joining this very worthwhile group. To find out more about it and the meeting, go to their website at www.neuroethicssociety.org.

As I write this column, sitting at my desk on the east coast of Florida (Ft. Lauderdale), I am thankful that hurricane Matthew just missed us last week. I am not at all thankful that it devastated Haiti then went just to our east and on up to bring very bad weather to northern Florida and up the coast to the Carolinas. Here, we had only wind and rain gusts all day Wednesday, but no damage. We had all our hurricane shutters closed and had tested the portable generator, as the forecast was for Matthew to come very close and provide winds up to 140 mph. We learned from hurricane Wilma in 2005 just what a hurricane like that can do. At that time, we lost many trees (this is a heavily treed area), buildings were damaged, all electricity gone for a week and even stoplights blown away. And Wilma was a category 2-3 hurricane, not a category 4 like Matthew. We hope the rest of the season is quiet and that the folks up the coast recover quickly.

If you want to write an article for the *Carrier*, please contact me.

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