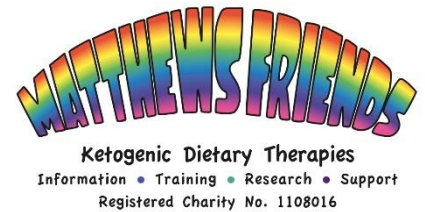


How Does the Ketogenic Diet Work

**Written by: Professor Robin SB Williams PhD FRSB
Matthew's Friends Medical Advisory Board
Professor of Molecular Cell Biology, Centre for
Biomedical Science, Royal Holloway University of
London**



The ketogenic diet was initially discovered as a mechanism to mimic starvation leading to seizure control¹. There are several different types of ketogenic diet, including the classical diet², the Medium Chain Triglyceride (MCT) diet³, Modified Atkins Diet (MAD)⁴, and Low Glycaemic Index (LGI)⁵ diet. These diets generally involve the increased consumption of fats with reduced carbohydrate and protein intake. They commonly lead to the production of 'ketones' or 'ketone bodies' in the liver, that are byproducts of fatty acid breakdown. These ketones are transported throughout the body in blood, and pass into the brain⁶. Ketones are widely considered to provide one of the key mechanisms that lead to the reduction of seizures⁷. Ketones can be measured through several approaches, including in blood, urine and breath. Increased levels of ketones are often found during fasting whereby our own stored fat is used, and in nutritional ketosis (in a ketogenic diet) through dietary fats. Optimal therapeutic ketone levels for seizure reduction are very individual. Measuring ketone levels provides a rapid approach both to validating that individuals are following the diet and to establishing the optimal individual ketone level for seizure control.

How ketones reduce seizures is still widely debated. Many clinical experts and research scientists believe that ketones provide energy to the brain, and this increased energy supply reduces the chance of a seizure⁸, but this is difficult to prove. Alternatively, many studies have shown that ketones regulate the activity of specific enzymes in the brain to reduce overactivation that causes seizures⁹. These effects include altering activity of ion channels¹⁰, or regulating the function of neurotransmitters in the brain¹¹. Some studies have suggested that ketones may protect neurons from dying during a seizure¹² or regulate the expression of genes¹³ where both cell death and altered gene expression are thought to increase the occurrence of seizures. Therefore, the generation of ketones during a ketogenic diet may reduce seizures through several mechanisms, and ketones remain a highly important theory on how the ketogenic diet works to reduce seizures.

However, there is some evidence that ketone production as a result of the ketogenic diet may not be the only mechanism by which the diet reduces seizures. These include that levels of ketones in patients do not consistently correlate with seizure control¹⁴⁻¹⁸ and some studies have shown that ketones do not directly block seizures in laboratory experiments^{19, 20}. These ideas have led to the investigation of additional mechanisms that may be important in providing seizure control in ketogenic diets.

One broadly accepted mechanism of ketogenic diets is through a change in cellular metabolism²¹. This refers to changes in the way that the brain produces energy, as an adaption to reduced carbohydrate intake and lower blood glucose levels. Metabolic changes seen in the ketogenic diet include the increased breakdown of fats and reduced use of glucose as an energy source²². Indeed, some studies have shown that simply reducing glucose metabolism provides seizure control²³. Other metabolic studies have suggested that ketogenic diets may be effective by enhancing levels of a specific neurotransmitter, adenosine, to decrease brain over-activation^{24, 25}. Other studies have identified that ketogenic diets reduce activity of a key protein complex (mTORC1) that provides a metabolic mechanism to control brain hyperexcitability^{26, 27}. Numerous studies have also identified that ketogenic diets elevate number of mitochondria that are responsible for the production of energy, to stabilise brain energy levels²⁸⁻³⁰ from both ketones and other sources such as fats and proteins. More recently, a significant role for gut microbes has also been identified, where bacterial populations change following ketogenic diets and^{31, 32}, these bacteria break down fats in the gut to regulate

brain function and reduce seizures. Finally, specific fats provided in the MCT ketogenic diet such as decanoic acid, may play a direct role in seizure control, through increasing mitochondria^{33, 34}, directly inhibiting neurotransmitter receptor activity^{33, 35, 36}, and inhibiting mTORC1 activity²⁶. Therefore, there are several well-supported mechanisms by which ketogenic diets lead to a reduction in seizures, that focus on metabolic changes that result from altered dietary intake.

References:

1. Hohn S, Dozieres-Puyravel B, Auvin S. History of dietary treatment from Wilder's hypothesis to the first open studies in the 1920s. *Epilepsy Behav* 2019;101:106588.
2. D'Andrea Meira I, Romao TT, Pires do Prado HJ, Kruger LT, Pires MEP, da Conceicao PO. Ketogenic Diet and Epilepsy: What We Know So Far. *Front Neurosci* 2019;13:5.
3. Neal EG, Chaffe H, Schwartz RH, et al. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. *Epilepsia* 2009;50:1109-1117.
4. Mutarelli A, Nogueira A, Felix N, et al. Modified Atkins diet for drug-resistant epilepsy: A systematic review and meta-analysis of randomized controlled trials. *Seizure* 2023;112:77-83.
5. Sondhi V, Agarwala A, Pandey RM, et al. Efficacy of Ketogenic Diet, Modified Atkins Diet, and Low Glycemic Index Therapy Diet Among Children With Drug-Resistant Epilepsy: A Randomized Clinical Trial. *JAMA Pediatr* 2020;174:944-951.
6. Williams RSB, Boison D, Masino SA, Rho JM. Mechanisms of Ketogenic Diet Action. In: Noebels JL, Avoli M, Rogawski MA, Vezzani A, Delgado-Escueta AV, eds. *Jasper's Basic Mechanisms of the Epilepsies*, 5th ed. New York: Oxford University Press, 2024: 1635-1666.
7. Simeone TA, Simeone KA, Rho JM. Ketone Bodies as Anti-Seizure Agents. *Neurochem Res* 2017;42:2011-2018.
8. Veech RL. The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism. *Prostaglandins Leukot Essent Fatty Acids* 2004;70:309-319.
9. Williams RSB, Boison D, Masino SA, Rho JM. Mechanisms of Ketogenic Diet Action. In: Noebels JL, Avoli M, Rogawski MA, Vezzani A, Delgado-Escueta AV, eds. *Jasper's Basic Mechanisms of the Epilepsies*, 5th ed. New York: Oxford University Press, 2024: 1635-1666.
10. Kadowaki A, Sada N, Juge N, Wakasa A, Moriyama Y, Inoue T. Neuronal inhibition and seizure suppression by acetoacetate and its analog, 2-phenylbutyrate. *Epilepsia* 2017;58:845-857.
11. Juge N, Gray JA, Omote H, et al. Metabolic control of vesicular glutamate transport and release. *Neuron* 2010;68:99-112.
12. Imamura K, Takeshima T, Kashiwaya Y, Nakaso K, Nakashima K. D-beta-hydroxybutyrate protects dopaminergic SH-SY5Y cells in a rotenone model of Parkinson's disease. *J Neurosci Res* 2006;84:1376-1384.
13. Shimazu T, Hirschey MD, Newman J, et al. Suppression of oxidative stress by beta-hydroxybutyrate, an endogenous histone deacetylase inhibitor. *Science* 2013;339:211-214.
14. Kacker S, Nordli DR, Jr., Phitsanuwoong C. Efficacy and tolerability of the modified Atkins diet in children with drug-resistant genetic generalized epilepsy. *Epileptic Disord* 2022;24:295-301.
15. Yellen G. Ketone bodies, glycolysis, and KATP channels in the mechanism of the ketogenic diet. *Epilepsia* 2008;49 Suppl 8:80-82.
16. Hartman AL, Vining EP. Clinical aspects of the ketogenic diet. *Epilepsia* 2007;48:31-42.
17. Zeng Y, Mu J, Zhou D. Calculation and management of ketogenic diet parenteral nutrition in super-refractory status epilepticus. *Acta Epileptologica* 2022;4:1-9.
18. Bough KJ, Yao SG, Eagles DA. Higher ketogenic diet ratios confer protection from seizures without neurotoxicity. *Epilepsy Res* 2000;38:15-25.
19. Thio LL, Wong M, Yamada KA. Ketone bodies do not directly alter excitatory or inhibitory hippocampal synaptic transmission. *Neurology* 2000;54:325-331.
20. Chang P, Augustin K, Boddum K, et al. Seizure control by decanoic acid through direct AMPA receptor inhibition. *Brain* 2016;139:431-443.
21. Rho JM, Boison D. The metabolic basis of epilepsy. *Nat Rev Neurol* 2022;18:333-347.
22. Effinger D, Hirschberger S, Yoncheva P, et al. A ketogenic diet substantially reshapes the human metabolome. *Clin Nutr* 2023;42:1202-1212.
23. Stafstrom CE, Ockuly JC, Murphree L, Valley MT, Roopra A, Sutula TP. Anticonvulsant and antiepileptic actions of 2-deoxy-D-glucose in epilepsy models. *Ann Neurol* 2009;65:435-447.
24. Masino SA, Li T, Theofilas P, et al. A ketogenic diet suppresses seizures in mice through adenosine A(1) receptors. *J Clin Invest* 2011;121:2679-2683.
25. Williams-Karnesky RL, Sandau US, Lusardi TA, et al. Epigenetic changes induced by adenosine augmentation therapy prevent epileptogenesis. *J Clin Invest* 2013;123:3552-3563.
26. Warren EC, Dooves S, Lugar E, et al. Decanoic acid inhibits mTORC1 activity independent of glucose and insulin signaling. *Proc Natl Acad Sci U S A* 2020;117:23617-23625.
27. McDaniel SS, Rensing NR, Thio LL, Yamada KA, Wong M. The ketogenic diet inhibits the mammalian target of rapamycin (mTOR) pathway. *Epilepsia* 2011;52:e7-11.
28. Bough KJ, Wetherington J, Hassel B, et al. Mitochondrial biogenesis in the anticonvulsant mechanism of the ketogenic diet. *Ann Neurol* 2006;60:223-235.
29. Noh HS, Lee HP, Kim DW, et al. A cDNA microarray analysis of gene expression profiles in rat hippocampus following a ketogenic diet. *Brain Res Mol Brain Res* 2004;129:80-87.
30. Hughes SD, Kanabus M, Anderson G, et al. The ketogenic diet component decanoic acid increases mitochondrial citrate synthase and complex I activity in neuronal cells. *J Neurochem* 2014;129:426-433.
31. Dalile B, Van Oudenhove L, Vervliet B, Verbeke K. The role of short-chain fatty acids in microbiota-gut-brain communication. *Nat Rev Gastroenterol Hepatol* 2019;16:461-478.

32. Lum GR, Ha SM, Olson CA, et al. Ketogenic diet therapy for pediatric epilepsy is associated with alterations in the human gut microbiome that confer seizure resistance in mice. *Cell Rep* 2023;42:113521.
33. Augustin K, Khabbush A, Williams S, et al. Mechanisms of action for the medium-chain triglyceride ketogenic diet in neurological and metabolic disorders. *Lancet Neurol* 2018;17:84-93.
34. Hughes SD, Kanabus M, Anderson G, et al. The ketogenic diet component decanoic acid increases mitochondrial citrate synthase and complex I activity in neuronal cells. *J Neurochem* 2014;129:426-433.
35. Chang P, Augustin K, Boddum K, et al. Seizure control by decanoic acid through direct AMPA receptor inhibition. *Brain* 2016;139:431-443.
36. Yelshanskaya MV, Singh AK, Narangoda C, Williams RSB, Kurnikova MG, Sobolevsky AI. Structural basis of AMPA receptor inhibition by trans-4-butylcyclohexane carboxylic acid. *Br J Pharmacol* 2022;179:3628-3644.