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Medium Chain Triglyceride (MCT) Ketogenic Diet and Its Role in Epilepsy

Muthmainah
Neuroanatomy Division, Department of Anatomy, Faculty of Medicine, Universitas Sebelas Maret (UNS) Surakarta

ABSTRACT

Brain mainly uses glucose as its energy sources; it can also use ketone bodies and free fatty acids for oxidative fuel. Decreased energy production in seizure is commonly caused by the lack of TCA cycle intermediates and acetyl-CoA. MCT diet induces ketosis and facilitates anaplerosis to provide intermediate substrates that can be used to support brain metabolism. MCT diet has been shown to help control seizure.

Keywords: Anaplerosis, epilepsy, ketosis, medium chain triglyceride (MCT)

ABSTRAK

Otak menggunakan glukosa sebagai sumber energi. Otak juga dapat menggunakan badan keton dan asam lemak bebas sebagai sumber energi oksidatif. Penurunan produksi energi dalam kasus kejang sering disebabkan karena kekurangan zat antara dan asetil-KoA dalam siklus asam trikarboksilat (siklus Krebs). Diet MCT dapat menginduksi ketosis dan anaplerosis untuk menghasilkan substrat antara dalam siklus Krebs yang dapat dipakai untuk menopang metabolisme di otak. Diet MCT terbukti dapat membantu mengontrol kejang. **Muthmainah. Peran Diet Ketogenik *Medium Chain Triglyceride* (MCT) pada Epilepsi**

Kata kunci: Anaplerosis, epilepsi, ketosis, *medium chain triglyceride* (MCT)

INTRODUCTION

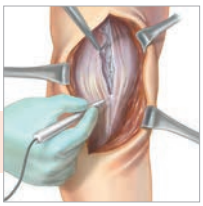
Brain mainly uses glucose as a source of oxidative fuel.[1] To meet the energy requirement, glucose must be transported continuously because fuel storage capacity in the brain is very limited. Impairment of glucose metabolism can cause hyperexcitability of the neuron which can be seen as epilepsy and delayed maturation of brain.[2]

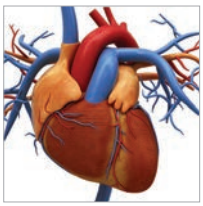
It is reported that brain can use fatty acid acids as its oxidative fuel. Ebert, et al, (2003) revealed that brain can fulfill 20% of its energy from oxidation of a medium-chain fatty acid.[1] Zhang, et al, (2013) reported that in case of prolonged starvation, ketone bodies can also substitute the role of glucose.[3] Edmond, Robbins, Bergstrom, Cole, & de Vellis (1987) revealed that neuron, astrocyte, and oligodendrocyte cultures were able to use glucose, ketone bodies, and free fatty acids for oxidative processes. All cells utilized ketone bodies more than they utilized glucose.[4]

Dysfunction of metabolic processes also contributes to seizure-associated condition such as several forms of epilepsy.[5] Decreased energy production can induce seizure in epileptic brain, commonly due to lack of tricarboxylic acid (TCA) cycle intermediates and acetyl-CoA.[5] Anaplerosis will refill the deficiency by providing intermediate substrates to the cycle such as pyruvate derived from glucose or propionyl CoA from even medium chain triglyceride (MCT).[5] Anaplerosis is a process to overcome energy depletion in seizures because it provides intermediate substrates for energy production.[6] Ebert, et al, (2003) revealed that administration of octanoate, an even-numbered MCT, support the oxidative metabolism in the brain by providing glucose derived from gluconeogenesis and facilitating anaplerosis. [1]

MCT diet is a variation of the classic ketogenic diet that allows higher proportion of carbohydrates intake but still preserves ketosis. It also allows more fruits and vegetables in the diet.[7] Chronic ketosis induced by ketogenic diet has been used to treat intractable seizures with a promising result.[8] In addition, Wlaz, et al, (2012) argued that caprilic acid which is the main constituent in MCT ketogenic diet was proven to show an acute anticonvulsant property.[9] Diet containing triheptanoin, an MCT with 7 carbon chain, exhibited an anticonvulsant effect on two chronic mouse models.[10] Administration of oral triheptanoin, an odd-chain MCT, showed an anticolvulsant effect on a syndrome-specific genetic mouse model of general epilepsy.[11] These findings suggest that MCTs have a significant potential for the treatment of seizure, in particular epilepsy.

Alamat Korespondensi *email: muthmainah.fkuns@gmail.com*





Medium Chain Triglyceride (MCT): Properties and Metabolism

Medium-chain triglyceride (MCTs) is comprised of saturated fatty acids which has 6 – 10 carbon chains length including hexanoic acid (C6:0, known as capronic acid), octanoic acid (C8:0, known as caprylic acid), and decanoic acid (C10:0, known as capric acid). Sometimes, dodecanoic acid (C12:0, common name lauric acid) is also considered as MCT. They were firstly used as a special source of energy within various clinical nutrition setting. Although dietary fat mostly contain long-chain fatty acids, MCTs can be found in some natural resources such as coconut or palm kernel oil and bovine milk. Compared to long-chain triglyceride, MCTs are different in the chemical and physical characteristic with smaller molecule size, lower melting point and less energy dense which influence their absorption and metabolism.[12] MCTs produce more ketones than long-chain triglycerides (LCT) meaning that they have higher ketogenic potential so that the amount of total fat needed in MCT diet is less than that of LCT, thus enabling the inclusion of larger amount of protein and carbohydrate. MCT are also more efficiently absorbed and transported directly from gastrointestinal tract to the liver by the portal vein.[13]

MCTs are more likely to undergo an oxidation and rather than fat, they behave more like glucose. Unlike long-chain fatty acids, MCTs can cross the mitochondrial membrane directly without using carnitine palmitoyltransferase (CPT) resulting in faster oxidation.[12,14] This also suggests that medium-chain fatty acids enter mitochondria in the form of carboxylate.[15]

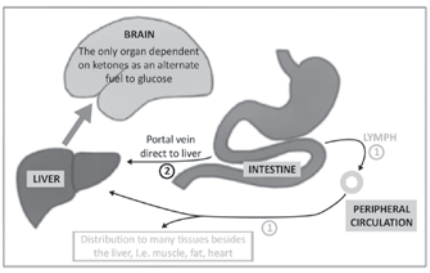


Figure 1. Absorption of medium chain fatty acids. While long chain fatty acids are distributed through the lymphatic and peripheral circulation, MCTs are directly absorbed to the liver through the portal vein.[16]

Prior to β oxidation, fatty acids must firstly be activated through ligation with coenzyme A (CoA). This process is catalyzed by ATP-dependent enzymes called acyl-CoA synthetases.[17] These enzymes are grouped based on the substrate specificities and subcellular locations. The chain length of fatty acids will determine the type of enzyme. Short chain acyl CoA synthetases work on acetate and proprionate and not on longer ones. Medium chain acyl CoA synthetases are known to act on monocarboxylic acids with 4-12 carbon chain. However, it is reported that the activity is best on octanoate.[17-19] Both enzymes are located in the mitochondrial matrix.[14,15,17,18,20] In addition, acetyl CoA synthetase which belongs to short chain enzyme can also be found in the cytosol of lipogenic tissue such liver and adipose tissue. Medium chain acyl CoA synthetase consists of four subtypes which are coded by different gene. Long chain acyl CoA synthetases which is located in cytosol acts both on saturated and unsaturated fatty acids with 10-20 carbon atoms.[17]

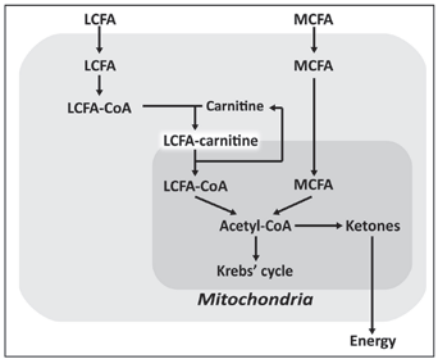


Figure 2. Beta oxidation of medium chain fatty acid. MCTs oxidation is simpler and faster compared to long chain fatty acids because, to enter the inner mitochondrial membrane, they do not need to be firstly activated by carnitine.[16] LCFA: long chain fatty acid; MCFA: medium chain fatty acid

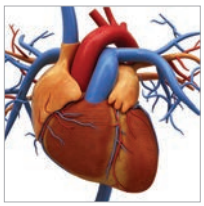
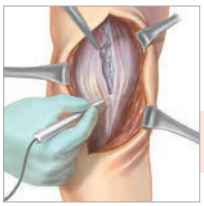
After being activated in the mitochondrial matrix, medium-chain fatty acids enter the next cycle in β oxidation which consist of four enzymatic process in which the acyl CoA undergoes dehydrogenation, hydratation, second dehydrogenation, and lastly thiolytic cleavage.[20] The first reaction is the dehydrogenation of acyl CoA to 2- *trans*enoyl CoA which is catalyzed by medium-chain acyl CoA dehydrogenase. This enzyme is a homotetramer with one FAD bound per subunit non-covalently.[18,20] The second reaction is the hydration of 2- *trans*enoyl CoA to L-3-hydroxyacyl CoA catalyzed by Enoyl-CoA hydratases. The next step is the dehydrogenation catalyzed by 3-hydroxyacyl CoA dehydrogenase and lastly thiolytic cleavage by 3-ketoacyl CoA. The final product of this reaction is acetyl CoA for even MCTs while for uneven MCTs, the end results are acetyl CoA and proprionyl CoA.[18,20]

Medium Chain Triglyceride (MCT): Its Potential Significance In Seizure Control

Current research has been focusing on increasing anaplerosis in the brain to avoid seizure.[6] The underlying concept is that in chronic epilepsy, the number of TCA cycle intermediates are decreased. During seizure, release of neurotransmitter such as glutamate and aspartate are higher due to increased neurotransmission. Thus, providing TCA cycle with intermediates through anaplerosis can be a potential approach in epilepsy therapy.[5] Medium chain triglyceride (MCT) was able to provide intermediate substrates from anaplerosis.[5]

Valencia, *et al*, (2012) revealed that dietary triheptanoin is metabolized into plasma heptanoate which further can enter the liver or directly cross the blood brain barrier.[2] Infusion of [5,6,7-13C3] heptanoate showed that in the liver, heptanoate will be oxidized into acetyl CoA which later is converted into glucose via gluconeogenesis. Alternatively, the liver will use the acetyl and proprionyl CoA to produce [3,4,5-13C3]C5-ketones which will be released to the bloodstream. Glucose and keton bodies will both be transferred to the brain for oxidative fuel. On the other hand, plasma heptanoate can directly enter the brain by passive diffusion. The brain can utilize [5,6,7-13C3]heptanoate and [3,4,5-13C3]C5-ketones to produce acetyl CoA and [1,2,3-13C3]propionyl-CoA. Acetyl CoA then enters the tricarboxylic acid (TCA) cycle while propionyl CoA is converted into succinyl-CoA. The later, subsequently also enter the TCA cycle. Another important feature is the fact that glutamine level is higher compared to glutamate which means that heptanoate or the derivatives are metabolized directly in brain.[2] This finding suggests that heptanoate, either directly metabolized in the brain or in the periphery could support energy metabolism through anaplerosis.

A study on octanoate, using nuclear magnetic resonance spectroscopy revealed that

this component contributes to the overall energy production in the brain.[1] Infusion of [2,4,6,8-13C4] octanoate increased blood glucose which will subsequently undergoes oxidation in the brain. The glucose is derived from gluconeogenesis in the liver. It also revealed that octanoate plays a significant role in brain anaplerosis which occurred in astrocyte.[1] Astrocytes play several roles in the brain including fatty acid and the brain energy metabolism.[21] Similar to neuron, astrocytes are also able to oxidize glucose and lactate because their processes contain mitochondria. However, unlike neurons which mainly depend on oxidative pathway to fulfil the energy requirement, astrocytes exhibit lower rate of oxidative metabolism and tend to use glycolytic pathway resulting in release of lactate in the extracellular space.[22]

Former study revealed that increased ketones could alter the seizure threshold in animal.[23] Upregulation of TCA cycles-related enzymes gene expression, oxidative phosphorylation and glycolysis that enhanced brain metabolism have been found after ketogenic diet administration.[6] In addition, during high level of neuronal activity such as in seizure, the loss of glutamate, a derivate of alpha ketoglutarate and the most prominent neurotransmitter, is increased. Anaplerosis provides this TCA cycle intermediate that substitutes this depletion. Thus, boosting the TCA cycle pathway can be an alternative strategy in seizure control.[6]

Conclusion

Impaired glucose metabolism contributes to the development of epilepsy. MCT ketogenic diet provides anaplerotic intermediates that can support brain metabolism. Administration of MCT diet has been shown to reduce seizure frequency and thus, can be used to help control seizure.

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