The urgent need for new metabolic (dietary) treatments of epilepsy

Epilepsy is a common neurological disease that is characterized by recurrent seizures due to the spontaneous excitatory firing of groups of neurons. Despite the increasing number of anti-seizure medications available, approximately 30% of patients remain treatment resistant and still suffer from epileptic seizures. The processes that lead to spontaneous seizures are complex. Many physiological processes can be out of balance and can promote seizures, such as the levels of excitation vs. inhibition, but also inflammation and impairments in energy metabolism. All current anti-seizure drugs dampen the crosstalk between the cells in the brain, in attempt to avoid overexcitation of cells which can lead to seizures. This suggests that new effective treatments should target different processes other than excitability of neurons to help people with treatment-resistant epilepsy. Metabolic therapies such as the ketogenic diet and various versions thereof are promising approaches, as they do not dampen neuronal activity and thus do not slow thinking processes or make people with epilepsy tired. These therapies have improved remarkably over the last 30 years and have been shown to be effective in multiple clinical trials in drug-resistant patients, mostly children but also some adults. However, these dietary regimens are not free of side effects. They require medical and dietary supervision, restrict food choices and intake. They are also costly. Thus, many people with epilepsy are unable to follow the strict dietary treatment regimens. Therefore, I suggest that new improved metabolic therapies are urgently needed, which should be more effective in drug-resistant epilepsy than drugs that just dampen the excitability of the brain. To develop such new therapeutics, it is important to understand the mechanisms that initiate and propagate seizures.

Metabolic impairments in brain can promote epileptic seizures

The processes that lead to spontaneous seizures are complicated. Many physiological processes can be out of balance and can promote seizures, such as the levels of excitation vs. inhibition, but also inflammation and impairments in energy metabolism. This article attempts to explain the changes found in brain metabolism in between seizures compared to a “healthy” brain. Most living cells and especially brain cells rely on ATP, a powerful fuel that supports processes in
cells that require energy. For example, cells need energy to survive, to communicate with each other, to fight against injury and regenerate. Very importantly, our cells are surrounded by membranes, which require ATP to maintain a certain (electro-chemical) potential. This potential is again important for survival of the cells and in neurons it allows communication. In simple terms when the membrane potential is lost, neurones become excited and start firing. If this happens in certain groups of neurons, this overexcitation can initiate an epileptic seizure, which can spread to other areas of the brain and some cases involve the whole brain. Because ATP is vital to maintain membrane potentials, it is thought by many researchers, including myself, that providing sufficient ATP to the brain is crucial in people with epilepsy to prevent seizures.

Under normal circumstances the brain relies on glucose and its metabolism to produce ATP. Most of the cellular ATP is generated by mitochondria, which are found in most cells. Mitochondria are little powerhouses which supply ATP through complicated biochemical processes, such as the Krebs cycle and the electron transport chain (Fig. 1). Thus, for a healthy organism it is important that all the processes that produce ATP are intact.

Figure 1:

Growing evidence shows that dysfunction of metabolic processes in the brain can contribute to epileptic seizures. This includes impairments in glucose uptake into the brain and energy metabolism in mitochondria. This is supported by the fact that epileptic seizures can occur in people with genetic defects that result in insufficient uptake of glucose into the brain or deficiencies in mitochondria. Ultimately these defects lead to an inability to produce ATP, the
main fuel needed in cells for survival and stabilisation of membrane potentials which is needed to avoid the generation of seizures. These genetic imperfections can be passed to offspring. Moreover, in people and animals who developed epilepsy in response to brain injuries, problems in brain metabolism have been repeatedly described. Using modern brain imaging techniques many studies have shown that local glucose uptake is decreased in “epileptic hotspot brain areas” in between seizure activity \(^2^\); \(^3^\). This has also been shown in rodent epilepsy models. Thus, there is reason to believe that therapies aimed at increasing brain energy can be effective in people with epilepsy who do not get relief from seizures from the current medications available \(^4^\).

**What are the options to boost brain energy metabolism?**

**Current ketogenic therapies**

Current metabolic dietary approaches to treat epilepsy include the ketogenic diet, the modified Atkins diet and various versions thereof \(^1^\). The classic ketogenic diet consists of mainly long-chain triglycerides and is given in a 4:1 (wt:wt) ratio with 4g of fat eaten with only 1g of carbohydrate and protein. This ratio can be lowered to 3:1 or 2:1 or even 1:1 such as in the modified Atkins diet, depending on seizure control and tolerability. Also, slightly more carbohydrates can be consumed while doing the medium chain triglyceride (MCT) ketogenic diet. In some ketogenic diets, 50-60% of calories are from medium chain triglycerides (MCTs), these are oils that contain mostly triglycerides of eight or 10 carbon fatty acids, octanoate and decanoate. These MCTs, are more ketogenic (meaning they produce more ketones) than the long-chain triglycerides that are typically found in our food \(^5^\). Another alternative is the low glycemic index diet, in which higher amounts of carbohydrates with low glycemic index are allowed. Several controlled studies show that these high fat/low carbohydrate diets are effective in many children with epilepsy and some of the children remain seizure-free after stopping dietary treatment \(^1^\). Some adults also experience reduction in seizures. As mentioned above, the diet regimens are strict, which makes them very difficult to follow, especially for adults who are used to freely choose their food. In addition, these dietary approaches require both dietary and medical supervisions which are not accessible in many countries.
Ketogenic diets and their variations are thought to be anticonvulsant through various mechanisms. Importantly, due to the low carbohydrate intake with these diets, blood glucose levels constantly remain in the lower end of the normal range. This appears to help prevent seizures, because the inhibition of glucose metabolism in rodent seizure models can also block seizures, while high blood sugar levels promote seizures\(^6\). Moreover, when glucose is in short supply, the liver turns fats into ketones, which are then excreted into the blood. When blood ketone levels are high, human and rodent brains use substantial amounts of ketones instead of using only glucose\(^7\). ATP can be produced from ketones and can provide the energy needed for normal brain function. This demonstrates that alternative fuels, such as ketones, can be effective fuels and prevent seizures when glucose metabolism is impaired, such as in an “epileptic” brain.

**Even medium chain fats as anticonvulsants?**

In patients on the MCT ketogenic diet the blood levels of the medium chain fatty acids octanoate and decanoate, reach near millimolar amounts. Moreover, medium chain fatty acids can diffuse directly into the brain and can be metabolised (references in \(^8\)). Thus, while taking MCTs, the production of ketones by the liver should not necessarily be needed to provide the brain with alternative fuels. Interestingly, several studies have demonstrated that specific medium chain fats can be anticonvulsant in various models *in vitro* and *in vivo*\(^9;10\), such as octanoate and decanoate. In addition, our laboratory has employed the oils (triglycerides) of these fats as a suitable formulation to avoid acid overload in patients and animals. My laboratory found that the triglyceride of decanoate effectively inhibited seizure generation in two different mouse models. This raises the hope that it may also block seizures in people with certain types of epilepsy\(^8\).

The anticonvulsant mechanisms of medium chain fats are likely due to the provision of alternative fuel to glucose and potentially reduced glucose metabolism. Indeed, we published evidence that the MCT of octanoate reduces the metabolism of glucose. In addition, the MCT of decanoate can fight oxidative stress and it improves mitochondrial function, which can further support the synthesis of ATP\(^8\).

Altogether these new findings raises the hope that MTCs may also block seizures in some people with epilepsy\(^8\). Please note, that it remains to be investigated in controlled clinical trials whether MCTs can provide seizure control in people. Until such results are produced it cannot be
recommended to add MCTs to a normal diet, as this can cause weight gain, diarrhoea and other side effects, including increases in seizures frequencies and severity.

Uneven medium chain triglycerides: Triheptanoin as an anticonvulsant

Triheptanoin is a synthetic MCT, namely the triglyceride of the seven carbon fatty acid heptanoate. It provides fuel (acetyl-CoA) directly to the mitochondrial Krebs cycle. In addition, it is also highly effective in boosting the Krebs cycle and the production of ATP within the brain (Fig 1). Triheptanoin is already in clinical trials to treat rare metabolic disorders, such as long-chain fatty acid metabolism disorders and various diseases affecting the brain. It is also used to provide fuel to the brain in disorders where glucose cannot be taken up (glucose transporter1 deficiency) resulting in seizures and sudden odd movements. My laboratory discovered that triheptanoin protected mice against seizures in different epilepsy models. Along with other researchers, we also showed that triheptanoin improved brain metabolism in models of epilepsy, in which glucose metabolism was perturbed. Based on the mouse seizure models, effects against medication-resistant seizures in humans are possible. My team is about to finish three controlled clinical trials with triheptanoin in adults and children with epilepsy in Australia. Some results are promising (data unpublished).

Conclusion:
Different variations of dietary or metabolic therapies can be effective in people with epilepsy. Although much improved, the current strict dietary regimes remain difficult. Work in several laboratories worldwide raises the hope that novel simple metabolic therapies become available within the next 5-10 years. To develop such new therapeutics, it is important to support further research in the laboratory as well as in clinics.


**Fig. 1. Metabolism of glucose and alternative fuels.** Glucose is the main energy substrate under physiological conditions. When oxygen is present, it is metabolized by a series of reactions into acetyl CoA, which then enters the Krebs cycle. The Krebs cycle oxidises the acetyl (C2) group and feeds electrons in the electron transport chain (boxes I-IV on the bottom), which then generates ATP. In epilepsy glucose metabolism is impaired as shown by the lines in red and ATP production is therefore limited. There are several alternative fuels (all boxed on the top of diagram) which can also be metabolised to acetyl-CoA in the brain and subsequently produce ATP. Moreover, these fuels can inhibit seizures in rodent models, most likely because they increase ATP levels, which are needed to stabilise neuronal membrane potentials. The ketogenic diet and medium chain triglycerides produce ketones from fats. Also, (even) medium chain triglycerides produce the medium chain fats, octanoate (C8) and decanoate (C10), which can directly generate acetyl-CoA without becoming ketones. Triheptanoin, a medium-chain fuel, produces heptanoate, which may be superior to the even medium chain fuels. It is broken down into two acetyl-CoA and other molecules. These molecules can improve the function of the Krebs cycle, by promoting the entry of acetyl-CoA into the cycle and eventually ATP synthesis.

**Glossary:**

ATP is the main fuel in cells needed for processes requiring energy.

Medium chain triglycerides (MCTs):-Typically they contain only even medium chain fatty acids, such as the eight and ten carbon long, octanoate and decanoate. They are naturally found in coconut oil.

Triheptanoin is also a medium chain triglyceride, but it contains the uneven fatty acid, heptanoate consisting of seven carbons. It is only found in small amounts in some seeds, but can be produced synthetically. It is not freely available for human consumption at this time.
Long chain fats and fatty acids are naturally found in vegetable oils and meat. They cannot be metabolised by the brain.

Ketones typically contain 4 carbons. In the absence of high glucose amounts, ketones are produced from long chain fats by the liver. Moreover, MCTs, octanoate and decanoate can be turned into ketones.

The brain can use glucose, ketones, medium chain fatty acids (including heptanoate, octanoate, decanoate) as fuels, but not long chain fatty acids (longer than 14 carbons).

Please note that this article is not meant to give medical advice. All additions of supplement or major changes in diet need to be discussed with your doctor.