BRAIN COMMUNICATIONS

SCIENTIFIC COMMENTARY

New developments for dietary treatment of epilepsy after a century of history for the ketogenic diet

This scientific commentary refers to 'The link between brain acidosis, breathing, and seizures: a novel mechanism of action for the ketogenic diet in a model of infantile spasms' by Choudhary et al. (https://doi.org/10.1093/braincomms/fcab189) **and 'K.Vita: a feasibility study of a blend of medium chain triglycerides to manage drug-resistant epilepsy' by Schoeler et al.** (https://doi.org/10.1093/braincomms/fcab160)

In July 1921, Wilder published two short papers on two consecutive days.[1,2] He first hypothesized the role of ketosis for fasting-related seizure control and suggested that a ketogenic diet (KD) would equally benefit epilepsy patients (27 July 1921).[1] Wilder then reported the successful use of the KD in three epilepsy patients (28 July 1921).[2] Following these publications, nine articles on the KD were published during the 1920s, involving more than 400 patients with epilepsy, confirming the initial hypothesis of the anticonvulsant effect of the KD.[3]

One century later, the KD therapy (KDT) is an evidence-based treatment for drug-resistant epilepsy with stronger evidence in children than in adults.[4] The KDT is not considered as a last chance treatment for drug-resistant epilepsy anymore. The recent international consensus on KDT stressed the conditions when early use would be beneficial due to a special reported efficacy for seizure control including infantile spasm syndrome (West syndrome).[5] If the clinical application for epilepsy patients is established, the KDT remains in the search of the underlying mechanism. Over the last 25 years, active translational research work led to the conclusion that several mechanisms are acting jointly to provide the antiseizure activity of the KDT. Ketosis might play a role but is not by itself the unique explanation of the effect of the KDT.[6,7] In addition to ketone bodies, the probable mechanisms acting in the KDT include GABAergic mechanism, modulation of noradrenergic and serotoninergic tone, glycolytic restriction, antiseizure effects of adenosine, mitochondrial ATP-sensitive potassium channels, anti-inflammatory properties and microbiome modification.[6,7]

One century later, it is impressive to see how the KDT remains an active field of research. Recently in *Brain Communications*, we have two examples. Choudhary et al.[8] explore a new mechanism of action of the KDT in a rodent model of infantile epilepsy (infantile spasm model), while Schoeler et al.[9] reported a first clinical use of medium chain triglyceride (MCT) in drug-resistant epilepsy patients.

Choudhary et al.[8] reported for the first time that the anticonvulsant effects of the KDT occurred through changes in respiration leading to intracerebral acidosis. Although acidosis is a common finding in patients on the KDT, the intracerebral acidosis was never demonstrated. It is established that acidosis has anticonvulsant effects, whereas alkalosis has the opposite effect. The use of new tools such as ^{31}phosphorus magnetic resonance spectroscopy as well as a supplementation by sodium bicarbonate, as a pH buffer, allowed the demonstration of the role of intracerebral acidosis in the anticonvulsant effect of the KDT. It is interesting to note that an infantile epilepsy model has been used. This might be useful for such investigation since the immature brain is particularly susceptible to fluctuations in acid–base states. In addition, this is more relevant to humans with a predominant use of the KDT in children and especially in infantile spasm syndrome.[5]

The second paper is a prospective open-label feasibility study in drug-resistant epilepsy patients investigating the safety of a medical food blend containing a unique ratio of decanoic acid and octanoic acid. This is the first clinical use of decanoic acid as an antiseizure medication. This follows previous experimental studies. The preclinical studies on decanoic acid have been inspired by the clinical use of the MCT KDT in drug-resistant epilepsy.[5] Based on the observation of a blood rise of ketone bodies as well as two fatty acids (decanoic acid and octanoic acid) in patients under MCT KDT, these compounds have been explored for

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their anticonvulsant properties revealing that decanoic acid, but not the ketones β-hydroxybutyrate or acetone, has antiseizure activity.[10] Decanoic acid acts indeed on the glutamatergic pathway though a non-competitive antagonism of the AMPA receptors.[10] The feasibility study found that two-thirds of children and adults involved in this clinical trial completed the study. Gastrointestinal side effects were the main cause of discontinuation. Without a significant ketosis, a reduction of the mean seizure frequency by 50% (95% CI: 39–61%) was observed. Interestingly, the seizure reduction was correlated with blood concentrations of decanoic acids.[9] Further studies are needed to demonstrate the efficacy of this blend in epilepsy patients.

These two examples illustrate that the KDT remains a source of inspiration despite its long history. The KDT is still explored to decipher the various components of the mechanisms of action producing the anticonvulsant effect. More than an improvement in our understanding, some mechanisms might be a source for new antiseizure treatment development. The identification of decanoic acid as an active component of the MCT KDT in the last few years has led to the development of a blend for clinical trials. More remains to be explored, understood and developed in the future with the KDT. In the epilepsy field, it remains to better understand the effect of KDT on epilepsy comorbidities and on epileptogenesis to develop effective clinical intervention. Other neurological indications of the KDT are sometimes cited such as brain tumours, Alzheimer disease, autism spectrum disorders, etc. These hypotheses have to be properly explored. A rigorous scientific approach and clinical development are needed to reach an evidence-based use of the KDT. Hopefully, we have a one-century history as an example.

Competing interests

The authors report no competing interests.

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