Mechanisms of action for the medium-chain triglyceride ketogenic diet in neurological and metabolic disorders

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High-fat, low-carbohydrate diets, known as ketogenic diets, have been used as a non-pharmacological treatment for refractory epilepsy. A key mechanism of this treatment is thought to be the generation of ketones, which provide brain cells (neurons and astrocytes) with an energy source that is more efficient than glucose, resulting in beneficial downstream metabolic changes, such as increasing adenosine levels, which might have effects on seizure control. However, some studies have challenged the central role of ketones because medium-chain fatty acids, which are part of a commonly used variation of the diet (the medium-chain triglyceride ketogenic diet), have been shown to directly inhibit AMPA receptors (glutamate receptors), and to change cell energetics through mitochondrial biogenesis. Through these mechanisms, medium-chain fatty acids rather than ketones are likely to block seizure onset and raise seizure threshold. The mechanisms underlying the ketogenic diet might also have roles in other disorders, such as preventing neurodegeneration in Alzheimer's disease, the proliferation and spread of cancer, and insulin resistance in type 2 diabetes. Analysing medium-chain fatty acids in future ketogenic diet studies will provide further insights into their importance in modified forms of the diet. Moreover, the results of these studies could facilitate the development of new pharmacological and dietary therapies for epilepsy and other disorders.

Introduction

The ketogenic diet is a high-fat, low-carbohydrate diet that was developed as a treatment for epilepsy.[1] The diet aims to mimic the metabolic profile of fasting by reducing blood glucose concentration and increasing blood ketone concentration because starvation has long been reported to reduce the frequency of seizures. Under normal dietary conditions, the brain uses glucose as an energy source; by contrast, during fasting conditions, ketones are used as the main energy source. Hence, starvation (associated with seizure control) induces ketone generation, which might be the therapeutic mechanism of action. Despite the common use of the ketogenic diet to treat epilepsy, the mechanisms underlying its efficacy have remained unclear. However, advances in our understanding of the mechanisms of action of medium-chain fatty acids have resulted in a paradigm shift in the hypothesis behind the mechanisms of the diet, away from ketones as a therapeutic mechanism and focusing on fatty acids instead, paving the way for novel dietary and drug therapies for epilepsy and other disorders.

There are two forms of the ketogenic diet. The so-called classic ketogenic diet provides 60–80% of dietary energy through long-chain fats, which have 16–20 carbon atoms.[2] This diet is particularly stringent, with very low carbohydrate content, and consequently, it is difficult to maintain. As such, an alternative medium-chain triglyceride (MCT) ketogenic diet was developed,[2] in which fats are provided though triglycerides comprising about 60% octanoic acid (an eight-carbon fatty acid) and about 40% decanoic acid (a ten-carbon fatty acid). By contrast with the classic ketogenic diet, only about 45% of dietary energy is provided by these medium-chain fats (allowing a larger carbohydrate component),[2] and the more rapid metabolism of the shorter fatty acids results in more efficient generation of ketones.

The MCT ketogenic diet is used worldwide to treat drug-resistant epilepsy, mainly in children,[1] but also in adults.[3,4] Both the classic and MCT ketogenic diets have garnered increased interest as potential treatments for other diet-sensitive disorders, including Alzheimer's disease,[5–7] cancer,[8–12] and diabetes.[13,14] As with epilepsy, the main therapeutic mechanism was assumed to occur through replacing carbohydrates with ketones as an energy source.[15] However, despite the efficacy of the ketogenic diet in controlling seizures in patients with epilepsy, several studies have shown a poor correlation between blood plasma ketone concentrations and seizure control,[16,17] and ketones do not acutely block seizure activity in an animal model.[18] An additional study[19] has shown seizure control in the absence of ketosis. These observations challenge the view that ketones alone have a role in seizure control and raise the question of the roles of other components of the diet, particularly fats that are provided at high levels in the diet. Additionally, several studies[20–23] have indicated that medium-chain fatty acids provided in the MCT ketogenic diet can have a direct action on seizure activity and mitochondrial function. The aim of this Review is to describe the most recent advances in our understanding of the mechanisms of action of the MCT ketogenic diet in relation to epilepsy and to other disorders.

Metabolism of medium-chain triglycerides

Dietary triglycerides (provided as a supplement in the MCT ketogenic diet) are broken down in the gastrointestinal tract by lipases that preferentially hydrolyse medium-chain esters over long-chain esters (figure 1).[24] MCTs are hydrolysed to medium-chain fatty acids (fatty acids with six to 12 carbon atoms), which are then absorbed directly through the gut wall and transferred to the liver, where the medium-chain fatty

acids (eg, decanoic acid and octanoic acid) are rapidly metabolised through β-oxidation. Metabolism of these fatty acids mainly results in the generation of three major ketones, β-hydroxybutyrate, acetoacetate, and acetone (collectively called ketone bodies).[24] These ketones and any fats that escape metabolism are distributed through the blood in the circulatory system. The brain is thought to be primarily dependent on glucose as an energy source, and secondarily on hepatically derived ketone bodies. However, medium-chain fatty acids are able to cross the blood–brain barrier,[25,26] reaching brain concentrations that are more than 50% of those of fatty acids in plasma[25] and providing an alternative energy source for brain cells (neurons and astrocytes). Evidence suggests that medium-chain fatty acids have direct and differing effects on brain cell energy metabolism. Octanoic acid seems to undergo β-oxidation in astrocytes more easily than decanoic acid and consequently more readily produces ketones, whereas decanoic acid preferentially stimulates glycolysis, producing lactate,[27] which brain cells are able

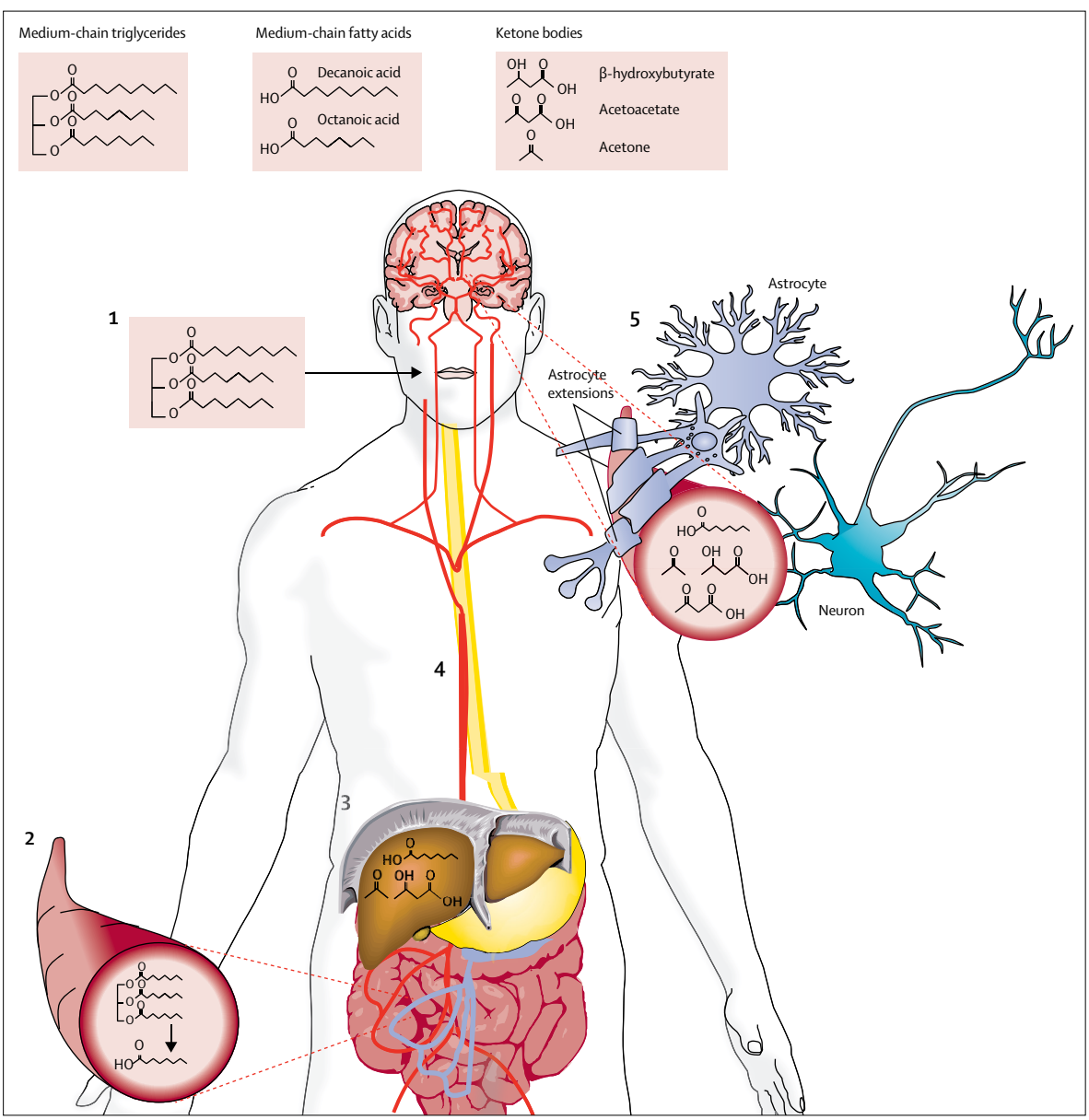

Figure 1: **Breakdown and circulation of dietary medium-chain triglycerides**
(1) Medium-chain triglycerides (containing decanoic acid and octanoic acid) are consumed as part of the medium-chain triglyceride ketogenic diet. (2) Medium-chain fatty acids (decanoic acid and octanoic acid) are liberated from the triglycerides in the intestine and then transferred to the liver, where (3) most of these medium-chain fatty acids are broken down to three ketone bodies (β-hydroxybutyrate, acetoacetate, and acetone). (4) Both free fatty acids and ketones are transported to the brain through blood circulation. (5) Fatty acids and ketones are transported across the blood–brain barrier, where they are available as a source of energy to brain cells.

to use as an energy source. Decanoic acid could promote the astrocyte–neuron lactate shuttle, which has been proposed to be the main energy source for brain cells; however, the importance of this shuttle as an energy source has been challenged by multiple lines of evidence, in which it was shown that oxidative glucose metabolism is underestimated and ATP generated from lactate is overestimated in most conditions.[28] Similarly, octanoic acid is preferentially oxidised (over decanoic acid) in brain cells,[29] suggesting a key metabolic role of neurons in the differential regulation of medium-chain fatty acid concentrations in the brain.

The medium-chain triglyceride ketogenic diet and epilepsy

Ketones and seizure control

Under normal dietary conditions, ketone bodies are found in blood plasma at very low concentrations, but their concentration increases under fasting conditions up to a total of 9 mmol/L and they can cross the blood–brain barrier via monocarboxylate transporters.[30] Under fasting conditions, ketones can provide the energy source for cells, and have been thought to be the key mechanism of action of the ketogenic diet in controlling seizure frequency in patients with epilepsy.[15,31] Patients with mutations of the glucose transporter GLUT1, which has a crucial role in transporting glucose from the circulatory system to the brain, respond well to both classic and MCT ketogenic diets because ketones are thought to replace the energy supply normally provided by glucose.[32] Glucose supplementation was found to diminish the anticonvulsant effects of the ketogenic diet in a mouse model of epilepsy,[33] suggesting that both fat administration and carbohydrate restriction in the ketogenic diet might be important in seizure control. Ketone bodies probably affect aminoacid metabolism, either directly as substrates or indirectly, resulting in changes to GABA and glutamate concentrations.[34] But do ketones have any direct or indirect effects on synaptic transmission or intrinsic neuronal excitability? The ketones β-hydroxybutyrate and acetoacetate do not affect ionotropic GABA(A) receptors or glutamatergic (AMPA and NMDA) receptors at therapeutically relevant concentrations,[35] while the ketones acetone and β-hydroxybutyrate only affect GABA(A) receptors and glycine receptors at very high concentrations (>100 mmol/L).[36] Nevertheless, ketones have been suggested to be able to compete with chloride at the vesicular glutamate transporter, decreasing vesicular glutamate content and consequently glutamatergic transmission.[37] Additionally, high concentrations of acetoacetate (>10 mmol/L) have been shown to inhibit voltage-dependent calcium channels in pyramidal cells of the hippocampus, resulting in reduced excitability in the hippocampus.[38] However, in rat models, ketones at high concentrations (≤10 mmol/L) have no direct effects on seizure-like activity induced in hippocampal slices by applying the GABA(A)-receptor antagonist pentetrazol,[18] or exposing them to low external magnesium. Despite a possible effect on glutamatergic transmission, the evidence, therefore, does not support a direct action of ketones on seizure activity.

However, ketones can have indirect effects on neuronal and network excitability, and anticonvulsant effects have been shown in some rodent models of seizure.[39–41] Switching from glucose to ketones as an energy source has also been suggested to result in a hyperpolarisation of neurons and a reduction in neuronal excitability. One indirect mechanism could be the reduction in ATP production from glucose oxidation, opening ATP-sensitive potassium channels;[42] in particular, the ketone β-hydroxybutyrate has been proposed to modify seizures through this pathway in addition to GABA(B) receptor signalling in a model of seizures in *Drosophila*.[43] Other possible indirect mechanisms include inhibition of the mitochondrial permeability transition pore, which has been implicated in mitochondrial dysfunction and neuronal death, and inhibition of adenosine kinase, thereby increasing adenosine levels and activating the inhibitory adenosine A1 receptors.[39,40] Moreover, ketones have been implicated in epigenetic effects that could be disease modifying in patients with chronic epilepsy, possibly through an action on adenosine metabolism.[44,45] Overall, the evidence that ketones can have an effect on seizure control is mixed, and this reduced seizure activity probably occurs through indirect metabolic effects.

Medium-chain fatty acids as a direct mechanism for seizure control

Research on use of MCTs in the ketogenic diet has provided important insights into the roles of fatty acids in seizure control. The efficacy of decanoic acid in seizure control has been shown in experiments in rats in which seizure-like activity was induced in hippocampal slices, either with pentetrazol or with perfusion of artificial CSF containing no magnesium.[18] Importantly, in these experiments, decanoic acid blocked seizure-like activity within 30 min of application in both models of seizure-activity induction, while ketones (β-hydroxybutyrate and acetone) did not.[18] Decanoic acid also increased seizure thresholds in animal models of acute seizures using both the 6 Hz stimulation test (a model of drug-resistant seizures)[46] and the maximal electroshock test (a model of tonic–clonic seizures),[25] although it was not effective in blocking pentetrazol-induced seizures in vivo (proposed to be a model of absence seizures). These experiments support a direct role of decanoic acid in in-vivo seizure control.

An important step in understanding the role of decanoic acid in seizure control was the discovery that decanoic acid can directly and selectively inhibit AMPA receptors in animal models (figure 2).[18] These receptors are key components in the generation of seizures[47] and can be blocked by micromolar concentrations of decanoic acid.[18] The mean concentration of decanoic acid in blood

from patients with epilepsy who receive the MCT ketogenic diet is around 157 µM, whereas no decanoic acid was found in individuals not on the diet.[48] An animal study[25] showed that decanoic acid rapidly and easily crossed the blood–brain barrier after ingestion. It is therefore likely that, in patients with epilepsy on the MCT ketogenic diet, decanoic acid would reach sufficient concentrations in the brain to reduce excitation and thereby provide reduced seizure frequency. This decanoic acid-dependent AMPA receptor inhibition shows enhanced inhibition during synaptic activation (when neurons are depolarised) and is non-competitive to glutamate;[18] it is also likely to be receptor-isoform specific, and thus might provide a strong basis for therapeutic efficacy. Direct inhibition of AMPA-receptor activity has been well established as an effective therapeutic mechanism in focal seizures and generalised tonic–clonic seizures, and the antiepileptic drug perampanel acts directly on AMPA receptors but at a different site from decanoic acid.[49,50] As such, the effects of decanoic acid seen in animal models are likely to be a direct result of AMPA-receptor inhibition.

Octanoic acid is the most abundant fatty acid when the MCT ketogenic diet is supplied, and is found in concentrations of about 310 µM in the plasma of patients with epilepsy.[48] Animal studies have investigated its role in seizure control. In one series of experiments, acute oral dosing with increasing levels of octanoic acid increased the threshold for induction of myoclonic and clonic convulsions in rats.[26] In a mouse model using 6 Hz stimulation to induce seizures, octanoic acid administered orally (by gastric gavage) also significantly increased the seizure threshold in an adenosine-receptor-dependent manner under reduced blood glucose concentrations.[51] However, in the same seizure model, this therapeutic effect was not seen in animals that received dietary octanoic acid-containing triglycerides when glucose levels were not controlled.[46] Octanoic acid had no inhibitory activity on AMPA receptors at concentrations found in patients with epilepsy on the MCT ketogenic diet,[18] suggesting that the potential anti-seizure effect was more likely to occur through indirect effects on adenosine receptors. However, in animal studies, novel branched octanoic acid derivatives, such as 5-methyloctanoic acid, provide both in-vitro and in-vivo seizure control and AMPA-receptor inhibition.[18,20,21]

Medium-chain fatty acids as an indirect mechanism for seizure control

An alternative mechanism for the effect of the MCT ketogenic diet on epilepsy arises from beneficial effects on brain energy metabolism. The diet causes alterations in glycolysis or mitochondrial function, or both, after which increasing ATP availability leads to an increase in seizure threshold.[52] Although long-chain fatty acids can uncouple mitochondria, potentially decreasing ATP production and lowering the seizure threshold (although

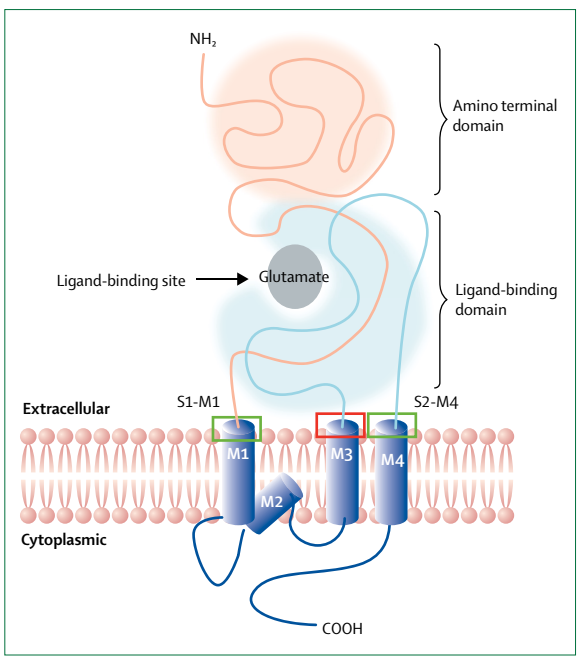

Figure 2: **Schematic representation of binding sites on AMPA receptors**
AMPA receptors occur as heterotetramers. Individual subunits comprise a large extracellular amino (NH_2) terminal domain and a glutamate ligand-binding domain, three transmembrane domains (M1, M3, and M4), and one re-entry loop (M2). The proposed site for decanoic acid on the M3 domain (red box) is distinct to those of perampanel at the linker regions (S1-M1 and S2-M4; green boxes) in the M1 and M4 domains. The carboxy terminal (COOH) resides in the cytoplasmic domain.

mitochondrial uncoupling can also have a paradoxical neuroprotective effect),[53–55] medium-chain fatty acids are much less likely to have a physiological role as uncouplers.[24] Clinical studies[56,57] into the effects of ketogenic diets in patients with mitochondrial disorders report substantial improvements in seizure control. This effect might be partly due to an action of decanoic acid on the peroxisomal proliferator-activated receptor γ (PPARγ),[23,58] resulting in enhanced mitochondrial function by stimulating mitochondrial biogenesis and increasing mitochondrial complex I activity.[23] Decanoic acid is a recognised PPARγ agonist, which elicits neuronal mitochondrial biogenesis (figure 3).[59–61] Similar results have been shown in an in-vivo model,[46] in which rats given a diet including decanoic acid-containing triglycerides had increased brain mitochondrial function and ATP synthesis capacity. Additionally, one study in mice[62] confirmed a synergistic effect of PPARγ agonists with the ketogenic diet in an in-vivo model of seizures. This mechanism of increased brain mitochondrial function seems to be specific to decanoic acid and is unlikely to be shared by octanoic acid, the other major component of the MCT ketogenic diet. In studies using animal or human-derived cell lines, octanoic acid does not activate PPARγ[59] or enhance levels of mitochondria in vitro,[23] and octanoic acid-containing triglycerides do not enhance mitochondria function in vivo.[46] Additionally,

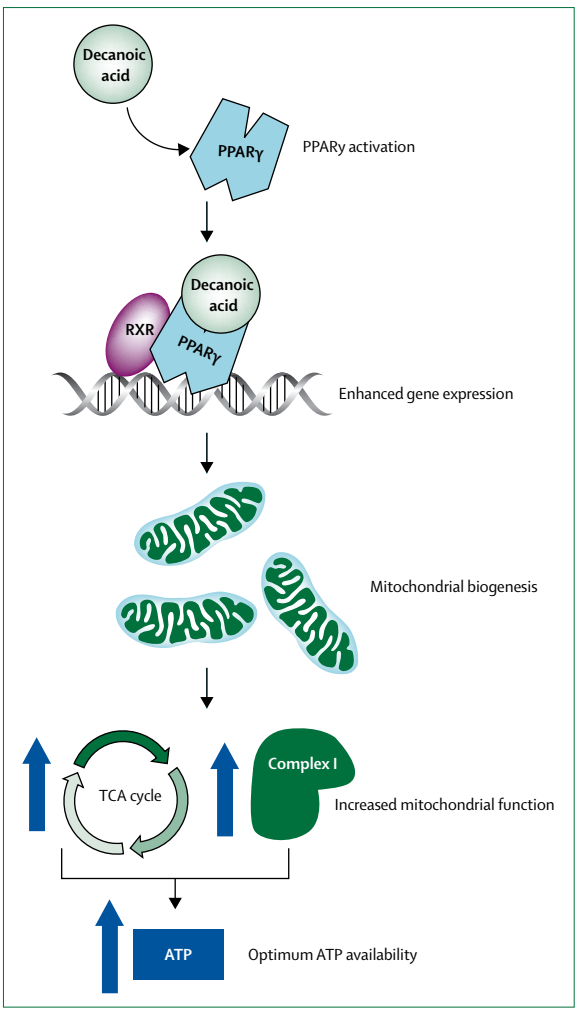

Figure 3: **Schematic representation of stimulating mitochondrial biogenesis with decanoic acid**

Decanoic acid binds PPARγ; this complex (with the retinoid X receptor [RXR]) can then bind target DNA to elevate gene transcription and enhance gene expression, which is thought to trigger mitochondrial biogenesis. Increasing the amount of mitochondria in a cell leads to elevated activity of the tricarboxylic acid (TCA) cycle and complex I (a component of the electron transport chain in mitochondria), resulting in increased ATP availability. PPARγ=peroxisome proliferator-activated receptor γ.

decanoic acid does not affect glycolytic enzymes, suggesting limited contribution to its anticonvulsant properties.[46] These studies indicate that, in the MCT ketogenic diet, decanoic acid rather than octanoic acid might have a role in seizure control.

Although these direct and indirect mechanisms identified in animal models have yet to be explored in human beings, their identification is likely to trigger an increasing interest in fatty acids as a therapeutic mechanism of the ketogenic diet. As such, plasma fatty acid concentrations (especially medium-chain fatty acids) are likely to be monitored in future clinical MCT ketogenic diet studies. Further research will also be needed to examine the complex interactions in the brain between medium-chain fatty acids and ketones, and the role of both components in seizure control.

The medium-chain triglyceride ketogenic diet and other diseases

In addition to its use as a treatment for drug-resistant epilepsy, the MCT ketogenic diet is increasingly being considered as a potential treatment for a range of other indications.

Alzheimer's disease

The effect of ketones on metabolic activity in the brain[5,6] highlights the potential of the ketogenic diet as a treatment for metabolic changes underlying Alzheimer's disease. Reduced uptake and metabolism of glucose have been strongly linked to progressive cognitive and motor degeneration, as neurons starve because of inefficient glycolysis.[7] One study in rats[63] has shown that the direct application of the ketone β-hydroxybutyrate in relevant concentrations protects hippocampal neurons from amyloid-β toxicity. In another study,[64] 20 patients with Alzheimer's disease or mild cognitive impairment received a single oral dose of MCT, but only patients without the *APOE* ε4 allele showed enhanced short-term cognitive performance, indicating that *APOE* ε4 genotype might affect response to dietary treatments. Additionally, three studies[65–67] (including two randomised controlled trials) have reported that treatment with an MCT ketogenic diet benefited only patients with mild Alzheimer's disease who did not have an *APOE* ε4 allele that was associated with Alzheimer's disease. Furthermore, in a transgenic mouse model of amyloid deposition, both classic and MCT ketogenic diets improved motor function but not cognition.[68]

Strong evidence exists that amyloid β increases AMPA-receptor currents and triggers subunit internalisation; this evidence directly links glutamate receptor hyperactivity to neurotoxicity and memory loss in Alzheimer's disease. In rodent models, amyloid β has been shown to interact with β-adrenergic receptors, which regulate gene expression and the activity of other receptors, including AMPA-type glutamate receptors via the cAMP–protein kinase A signalling cascade.[69,70] Phosphorylation of AMPA-receptor GluA1 subunits by protein kinase A has been shown to increase channel opening probability in human tissue culture, resulting in augmented calcium entry into the cell, which can lead to neurotoxicity.[71] A study in rats[72] has shown that the addition of amyloid β to neuronal cultures causes neurotoxicity by strengthening calcium-dependent AMPA-receptor generated currents. This finding suggests that amyloid-β-induced excitotoxicity could contribute to the widespread neuronal death seen in Alzheimer's disease. In addition to ketones providing energy to glucose-resistant neurons, the MCT ketogenic diet might also improve neuronal survival through the inhibition of AMPA receptors by decanoic acid. There is evidence in

mice that amyloid β triggers the internalisation of GluA2 subunits, the only AMPA-receptor subunit type that confers calcium impermeability.[73,74] Internalisation of GluA2 could therefore further increase total postsynaptic calcium influx, which could further increase inflammation and neurotoxicity. In rats, amyloid β-induced internalisation of AMPA-receptor subunits has been suggested to be sufficient to reduce long-term potentiation and therefore be linked to memory loss in Alzheimer's disease.[75] A study[76] in patients has shown that loss of GluA2 precedes pathological marker (tangles) development in the brain. This effect would be augmented if the remaining postsynaptic subunits were blocked by AMPA-receptor antagonists. Further research is needed to determine a role for the MCT ketogenic diet and AMPA-receptor antagonists in the treatment of Alzheimer's disease.

Mitochondrial dysfunction has also been implicated in the pathogenesis of Alzheimer's disease. Structural abnormalities of mitochondria, imbalances in mitochondrial fission and fusion, and defective electron transport chain activity have been reported in a model of Alzheimer's disease.[77] Moreover, evidence in mice suggests that amyloid β accumulation is associated with toxic effects in mitochondria, including impaired energy homoeostasis and impaired electron transport chain complex activity, particularly of cytochrome c oxidase (also known as complex IV);[77] disrupted mitochondrial structure and dynamics;[78] and increased mitochondrial oxidative stress.[77,79] With mitochondria intrinsically linked to cell signalling, mitochondrial damage consequentially leads to cell death and might cause the synaptic degeneration seen in Alzheimer's disease. However, very few studies have investigated the therapeutic effects of the MCT ketogenic diet in light of mitochondrial function, although one in-vitro study[80] has reported the attenuation of deleterious amyloid β-induced effects on rat cortical neurons treated with coconut oil (containing high concentrations of MCT), observing increased cell survival and improved mitochondrial structure and size. Although the mechanisms of these observed effects remain unknown, there remains a potential for the role of medium-chain fatty acids in this context. In particular, decanoic acid, which has the ability to improve mitochondrial function (figure 3),[23,81] might prove beneficial in the amelioration of amyloid β-induced mitochondrial damage. Additionally, the role of decanoic acid as an antioxidant[23,82] and as a PPARγ activator[83] might provide insight into the molecular mechanisms underlying the observed improvement in mitochondrial function.

Cancer

Ketogenic diets have gained substantial interest as an adjunctive therapy in the treatment of cancer, with data available from animal models[8] and observational studies in patients;[9–12] however, evidence for clinical efficacy from randomised controlled trials is scarce. Cancer cells are often highly dependent on glucose as a substrate, relying on anaerobic glycolysis to provide ATP, known as the Warburg effect;[84] this dependence on glucose is exploited in tumour imaging, in which PET is used to measure uptake of fluorodeoxyglucose. The commonly accepted mechanism by which the ketogenic diet might aid in cancer therapy is that the decrease in circulating blood glucose, and the inability of tumours to use ketone bodies, result in reduced tumour growth or tumour regression.[85,86] Although this hypothesis remains the most accepted explanation for a mechanism of the ketogenic diet, several studies in animals and human-derived cell cultures[9,12,87] have suggested that the effect on tumour growth might not be solely caused by a decrease in blood glucose concentrations. Many tumours preferentially use glutamine as a substrate rather than glucose, but whether a ketogenic diet has any effect on such tumours is unknown and requires further investigation.

A link between the MCT ketogenic diet, AMPA receptors, and cancer treatment comes from studies showing that human glioblastoma cells express increased levels of AMPA receptors[88] and that inhibition of AMPA receptors suppresses migration and proliferation of glioblastoma multiforme cells[89] and other cancer cells.[90] Furthermore, the AMPA receptor-specific inhibitor perampanel, which binds at a different site to decanoic acid (figure 2),[18] has been shown to be a potentially chemotherapeutically active adjuvant in a single case study of glioblastoma multiforme cells treatment.[91] These studies suggest that AMPA-receptor inhibition with decanoic acid might provide an adjunctive cancer treatment.

Diabetes

Diabetes can be broadly split into type 1 diabetes, in which the pancreas does not produce enough insulin because of a combination of genetic and environmental factors, and type 2 diabetes, in which lifestyle choices including obesogenic diets rich in carbohydrates and saturated fats, together with insufficient exercise, lead to hyperglycaemia and insulin resistance.[92] Dietary interventions, including the MCT ketogenic diet, have been investigated as new therapeutic approaches, mainly in type 2 diabetes. In several studies, MCT ketogenic diets have been found to reduce serum lipid concentrations and improve lipid profiles, decrease body fat, and reduce total bodyweight in animals[13] and human beings,[14] and increase energy expenditure in human beings.[93] MCTs have also been shown to reduce insulin resistance and improve glucose tolerance in an animal model[13] and in patients with type 2 diabetes.[94] Although the exact mechanism of these effects remains unknown, these studies suggest a beneficial role of MCTs in the treatment of type 2 diabetes and associated glucose-sensitive metabolic disorders. Ketogenic diets in patients with type 1 diabetes are more restricted in their benefit than in patients with type 2 diabetes, with the scientific

	Study description	Intervention(s)	Study population	Location of lead centre	Expected date of completion*
NCT03075514	KDs as an adjuvant therapy in glioblastoma: a randomised pilot trial	Modified KD *vs* MCT KD	Glioblastoma	UK	March, 2018
NCT02825745	Use of Betashot in children and adults with epilepsy	MCT-based emulsion	Epilepsy	UK	December, 2017
NCT02516501	Impact of a KD intervention during radiotherapy on body composition	MCT-based emulsion	Neoplasms	Germany	June, 2018
NCT02021526	Triheptanoin (C7 Oil), a food supplement, for glucose transporter type I deficiency	Normal diet plus C7 oil *vs* C7 oil as part of KD	Glucose transporter type I deficiency	USA	June, 2019
NCT02426047	Medium-chain triglycerides as an adjunct to the modified Atkins diet for women with catamenial epilepsy	Modified Atkins diet plus MCT-based emulsion	Epilepsy	USA	March, 2018
NCT02912936	A medium-chain triglyceride intervention for patients with Alzheimer's disease	MCT in milk *vs* sunflower oil in milk	Alzheimer's disease	Canada	February, 2018
NCT02679222	Comparing the KD of coconut oil and different medium-chain triglycerides	Different MCT supplements	Healthy adults	Canada	December, 2016
NCT02709356	Medium-chain triglycerides and brain metabolism in Alzheimer's disease	Different MCT emulsions	Alzheimer's disease and healthy elderly people	Canada	July, 2017
NCT02409927	Effect of medium-chain triglyceride emulsification on ketogenesis in adults	Different MCT preparations	Healthy adults	Canada	September, 2014
NCT02551419	Proof of mechanism of a new ketogenic supplement using dual tracer PET	MCT in milk *vs* sunflower oil in milk	Adults with mild cognitive impairment	Canada	June, 2018

KD=ketogenic diet. MCT=medium-chain triglyceride. *Final data collection date for primary outcome measure.

Table: **Completed and ongoing clinical trials using medium-chain triglyceride ketogenic diets**

Search strategy and selection criteria

We selected references by searching PubMed for manuscripts published in English between Jan 1, 2010, and Sept 18, 2017, using the term "ketogenic diet" or "medium-chain triglyceride" and assorted combinations of the following terms: "epilepsy", "seizures", "antiepileptic drugs", "dementia", "neurodegenerative disease", "Alzheimer's disease", "diabetes", "cancer", and "tumour". We examined the reference lists within original research and review articles for additional references. We finalised the reference list on the basis of originality and relevance to the scope of this Review.

literature consisting of case reports of patients with type 1 diabetes and poorly controlled epilepsy, or anecdotal reports.[95] A major concern about implementation of any ketogenic diet in patients with diabetes, especially type 1, is the potentially life-threatening complication of diabetic ketoacidosis, because low insulin promotes fatty acid oxidation and ketosis.

Mitochondrial dysfunction has also been postulated to have a role in insulin resistance and, consequently, the pathology of diabetes. Patients with type 2 diabetes have been found to have impaired mitochondrial activity,[96] with alterations in function and morphology,[97] in addition to increased reactive oxygen species levels,[98] which is linked to insulin resistance. Genetic variations and alterations in gene expression of PPARγ coactivator-1,[99] the key regulator of mitochondrial biogenesis, have also been proposed to have a role in the pathogenesis of diabetes. In view of these findings, a role for decanoic acid as a PPARγ agonist might provide a therapeutic effect in the treatment of diabetes. As such, increasing mitochondrial biogenesis through decanoic acid treatment, in conjunction with improved mitochondrial function and increased antioxidant capacity, could form a vital defence against the deleterious effects of mitochondrial dysfunction in diabetes.

Conclusions and future directions

The MCT ketogenic diet is widely thought to function through the generation of ketones, which provide an alternative energy source for brain cells, and is considered a potential treatment for a range of disorders including epilepsy, Alzheimer's disease, cancer, and diabetes. However, the underlying mechanisms of the diet are still largely unknown. Understanding the role of AMPA receptors, PPARγ, and mitochondrial biosynthesis in relation to MCT ketogenic diet-responsive disorders might provide new therapeutic targets and facilitate the development of new pharmacological and dietary treatments (eg, different fatty acid content in MCT diets) or chemical modification of fats to reduce metabolism clearance. The proposed mechanism of AMPA-receptor inhibition, PPARγ activation, and mitochondrial biosynthesis provides a rationale for efficacy in other conditions, and several clinical studies are currently validating the use of the MCT ketogenic diet in the treatment of other disorders (table). Additionally, further clinical studies are needed to either decrease or mitigate potential adverse effects of ketogenic diets, such as the low-grade acidosis resulting from elevation in β-hydroxybutyric and acetoacetic acids.[100] Furthermore, whether other ketogenic diets, such as the classic diet, are also associated with elevated concentrations of medium-chain fatty acids remains to be elucidated, and

monitoring of these components in clinical studies will help to investigate these mechanisms. Validation of these fats provided in the diet as therapeutic targets might both improve and widen the use of the diet as a treatment for epilepsy, Alzheimer's disease, cancer, diabetes, and other disorders.

Contributors

All authors contributed equally to the preparation and writing of the manuscript. All authors approved the final version.

Declaration of interests

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