Therapeutic potential of triheptanoin in metabolic and neurodegenerative diseases

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Abstract
In the past 15 years the potential of triheptanoin for the treatment of several human diseases in the area of clinical nutrition has grown considerably. Use of this triglyceride of the odd-chain fatty acid heptanoate has been proposed and applied for the treatment of several conditions in which the energy supply from citric acid cycle intermediates or fatty acid degradation are impaired. Neurological diseases due to disturbed glucose metabolism or metabolic diseases associated with impaired β-oxidation of long chain fatty acid may especially take advantage of alternative substrate sources offered by the secondary metabolites of triheptanoin. Epilepsy due to deficiency of the GLUT1 transporter, as well as diseases associated with dysregulation of neuronal signalling, have been treated with triheptanoin supplementation, and very recently the advantages of this oil in long-chain fatty acid oxidation disorders have been reported. The present review summarises the published literature on the metabolism of triheptanoin including clinical reports related to the use of triheptanoin.

KEYWORDS
anaplerosis, epilepsy and neurodegenerative diseases, metabolic diseases, triheptanoin

1 | INTRODUCTION

Triheptanoin is a triglyceride of three odd-chain fatty acid (heptanoate, C7) is synthesised from castor bean oil originally used in the human food industry as a tasteless additive to dairy products or as an emollient in cosmetics. After cleavage by intestinal lipases heptanoate is absorbed by the gastrointestinal tract and metabolised predominantly in the liver. Because of its fast metabolism and anaplerotic potential triheptanoin use has been proposed for several diseases where enhanced energy production improves the clinical course of the disease. In recent years, the number of diseases treated with triheptanoin has steadily increased. Here, we will present an overview on the metabolism of this compound followed by the summary of the experience of triheptanoin supplementation in several metabolic and neurological diseases.

2 | METHOD

This review was based on a search of the MEDLINE database using PubMed as the search engine. The selected keywords triheptanoin and heptanoate were used for the literature search. In total 77 articles were reviewed.

2.1 | Metabolism of triheptanoin

In contrast to long-chain fatty acids, after ingestion the medium chain fatty acid octanoate (C8) diffuses easily
and directly to the venous system and subsequently to the tissues. Most of the circulating C8 fatty acids reach the liver where they can be directly metabolised. Due to the physical-chemical and structural similarities it is likely that undergoes a similar process. Intracellularly, C7 can cross the double mitochondrial membrane without the need of an active transport system and can enter the β-oxidation cycle producing two molecules of acetyl-CoA and one molecule of propionyl-CoA. The latter molecule can undergo carboxylation to methylmalonyl-CoA, an anaplerotic substrate for the citric acid or tricarboxylic acid cycle (TCA) and a substrate for complex II of the respiratory chain, thereby supporting mitochondrial energy production. The anaplerotic effect of propionyl-CoA also indirectly supports gluconeogenesis through increased ATP generation. Alternatively, heptanoate may undergo only one cycle of mitochondrial β-oxidation and the generated C5 fatty acids, which are redirected to the biosynthesis of the C5-ketone bodies β-ketopentanoate (BKP) and β-hydroxypentanoate (BHP). Once released into the bloodstream they cross the blood brain barrier and may be used as substrate for energy production in the absence of sufficient glucose. Heptanoate in peripheral tissues is converted to acetyl-CoA and propionyl-CoA via 3-oxoacid-CoA supplying the tissues with the required energy.

Triheptanoin is considered a strong anaplerotic substrate, replenishing the TCA cycle C4/C5 intermediate pool when deficient. Moreover, there is a relationship between the metabolism of heptanoate and the regulation of anabolic and catabolic pathways through the action of signalling cascades regulated by nutrients, AMP-mediated protein kinase (AMPK) and the mammalian target of rapamycin mTOR. In fact, activation of AMPK signalling cascade due to reduced TCA intermediates and the reduction of ATP stimulates AMPK signalling which leads to the inhibition of mTOR and the activation of catabolic processes.

**FIGURE 1** Schematic representation of the activation of AMPK and mTOR signalling by nutrients modified from Roe and Mochel. Heptanoate and anaplerotic reactions supply the citric acid cycle (TCA) with the required and additional substrates. This process activates mTOR signalling with the subsequent stimulation of synthetic pathways. In contrast, lack of TCA intermediates and the reduction of ATP stimulate AMPK signalling which leads to the inhibition of mTOR and the activation of catabolic processes.

**FIGURE 2** Schematic representation of the metabolism of triheptanoin. When heptanoic acid enters the mitochondria, it may undergo either one or two cycles of β-oxidation. In the first case, acetyl-CoA can serve as substrate for the TCA cycle and the C5 fatty acids can be used for the biosynthesis of C5 ketone bodies which are neuroprotective. The generated ATP can also inhibit the release of glutamate contributing to the prevention of ischemic strokes. On the other hand, after two cycles of β-oxidation the generated two acetyl-CoA units can enter either the TCA cycle or be used for the biosynthesis of C4 ketone bodies. The C3 unit represented by propionyl-CoA can be converted to succinyl-CoA and feed either the TCA cycle or directly the complex II of the respiratory chain. AR, anaplerotic reaction; ATP, adenosine triphosphate; BKP, β-ketopentanoate; BHP, β-hydroxypentanoate; CII, complex II of the electron transport chain; NADH/FADH₂, nicotinamide adenine dinucleotide/flavin adenine dinucleotide; TCA, citric acid cycle.
seizures occur when abnormal brain activity is spread in part of one brain hemisphere. In contrast, generalised forms of seizures exist. Focal seizures are localised to a very high.2 On the other hand, triheptanoin administered intraduodenally is first absorbed then metabolised by the liver.2

2.2 | Triheptanoin for the treatment of epilepsy and other neurological conditions

Epilepsy is the fourth most common neurological disorder in the United States12 reflecting abnormal brain electrical activity, affecting all age groups.13 Clinically, it manifests as seizures, periods of unusual behaviour or sensations and sometimes loss of awareness.14,15 Several forms of seizures exist. Focal seizures are localised to a part of one brain hemisphere. In contrast, generalised seizures occur when abnormal brain activity is spread in both hemispheres of the brain.16 To date more than 500 epilepsy-associated genes, which play a role in neuronal excitability, cortical development or synaptic transmission, have been described.15 Approximately one-third of the patients suffer from untreated epilepsy.17 However, most of patients can be treated either medications that aim to decrease the neuronal excitability,13,14 or by surgery, by neumodulation devices, and by dietary interventions such as the ketogenic diet or triheptanoin.14

Several epilepsy forms are characterised by impaired glucose metabolism, which leads to a lack of ATP and carbons to produce lipids and amino acids leading to seizures, the dysregulation of neuronal signalling due to the high energy need for the stabilisation of membrane potentials and the proper regulation of neural signalling.18

In epileptic brains, TCA intermediates may be deficient, leading to hyper-excitability.19 In this instance, C7 can serve as an alternative source of fuel. Indeed, either heptanoate itself or C5 ketone bodies after liver degradation can serve as useful source of energy for the brain.20,21 Specifically, studies on the mouse pilocarpine model of epilepsy highlighted that triheptanoin treatment decreases the reduction of malate and propionyl-CoA.19 Furthermore, enrichment studies with [U-13C6]-glucose have shown that in addition to its anaplerotic potential, triheptanoin is also able to improve glucose utilisation and increase otherwise impaired glucose oxidation in the interictal hippocampus.22

The neuroprotective activity of heptanoate can be attributed not only to the mechanisms of anaplerosis and stimulation of glucose metabolism but also to the antioxidant activity as measured in pilocarpine-induced status epilepticus mice.23 Indeed, triheptanoin prevented the reduction of hippocampal mitochondrial superoxide dismutase activity, plasma antioxidant status lipid peroxidation, neuronal degeneration in hippocampus after status epilepticus in mice.23 Heptanoic acid also protected cultured neurons against damage by oxygen glucose deprivation or N-methyl-D-aspartate receptor (NMDA).23 Because of these activities, triheptanoin has repeatedly been shown to have anticonvulsant effect in acute and chronic mouse seizure models.5,19,24,25 In children with medically refractory epilepsy the treatment was safe and tolerable, but efficacy was not assessed.20,26 The protective effect of triheptanoin on focal unaware seizure with treatment-resistant epilepsy was smaller and was observed in only one out of nine patients.20

The anaplerotic properties of triheptanoin also makes it an attractive possible treatment for several other neurological diseases,8 and has been studied in several rodent models of disease including Rett syndrome,27 amyotrophic lateral sclerosis amyotrophic lateral sclerosis (ALS)28,29 and Alzheimer disease.30 In human subjects it has been examined in Huntington disease.7,31 In particular, Adeneyeguh et al showed that based on magnetic resonance spectroscopy of patients brains, triheptanoin can correct the bioenergetic profile in the brain of patients with Huntington’s at an early stage of the disease.7 Finally, in a mouse model of Canavan disease, triheptanoin reduced oxidative stress, increased brain myelination and prevented the loss of oligodendrocytes.32

2.3 | The specific use of triheptanoin in Glut1 deficiency

Glut1 deficiency or G1D is a rare disease with an incidence of 1:90 000 newborns. It is an autosomal dominant disorder caused by a mutation in the SLC2A1 gene encoding the high affinity CNS GLUT1 transporter that transports glucose across the blood brain barrier. A defect of this transporter reduces energy production from glucose in brain cells, affecting cell development and brain function. The phenotype includes psychomotor retardation, permanent motor disorders and epileptic and non-epileptic paroxysmal episodes.33 Glycolysis in the brain directly generates energy and supplies acetyl-CoA for myelin synthesis and for neurotransmitter production.34 In addition, glucose derived
pyruvate is the starting substrate for gluconeogenesis via carboxylation.35 Treatment of disorders associated with impaired CNS glucose metabolism with anaplerotic substrates such as acetyl-CoA and propionyl-CoA has been proposed to bypass this block.35 In particular, heptanoate from triheptanoin can directly be metabolised to its end products in the brain, or in peripheral tissues that can be delivered to the brain as even or odd chain ketone bodies.33,35-38 A traditional ketogenic diet in G1D has been helpful in seizures control, but is suboptimal in controlling the associated movement disorder.33 However, ketogenic diet successfully controls seizure in G1D in only two-thirds of cases, hypothesised to be due to a counterintuitive decrease of glucose availability for the brain.1 In contrast, triheptanoin improves brain glucose depletion in G1D, improving neurophysiological performance, cerebral metabolic rate and reducing spike-wave seizures.1 The hydrolysis of triheptanoin after ingestion produces also free glycerol which is used as precursor for gluconeogenesis resulting in higher circulating glucose, which is further absorbed and oxidised in the brain.35 In another study, up to 90% of patients showed an improvement in non-epileptic paroxysmal manifestations with normalisation of the brain bioenergetics profile.33 This finding was associated with an increase of the Pi/PCr ratio, indicative of an increase of ATP production in brain mitochondria.33

Unfortunately, very recent results in a Phase 3 study of triheptanoin (UX007) for the treatment of G1D showed no statistically significant reduction in paroxysmal movements with triheptanoin treatment compared to placebo, resulting in the discontinuation of the development plan for the application of triheptanoin in G1D.

### 2.4 Triheptanoin in long-chain fatty acid disorders

Triheptanoin has also been proposed and studied for the treatment of long-chain fatty acid oxidation disorders (lc-FAOD) based on the hypothesis that energy deficiency in fatty acid oxidation patients may be exacerbated by the depletion of catalytic intermediates of the TCA and would thus benefit from the anaplerotic effect of triheptanoin.39,40 In this regard, several clinical trials are either still ongoing41 (actualised 2019) or completed.42 In total, triheptanoin has been shown to positively impact three of the major clinical manifestations of lc-FAODs: hypoglycaemia, cardiomyopathy and rhabdomyolysis.39,40,42-44 Triheptanoin supplementation compared in a double blind study with trioctanoate over 4 months increased left ventricular ejection fraction and decreased left ventricular wall mass at rest and reduced the heart rate during exercise.43 It has also successfully been utilised in open label emergency studies as rescue therapy for cardiogenic shock in these disorders.44,45 Finally, triheptanoin improved the muscular phenotype of lc-FAOD including reducing episodes of rhabdomyolysis and the number of hospitalisations over a 2-year period.42,46

In a mouse model of very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency (VLCAD−/− mouse), the anaplerodic effect of triheptanoin did not manifest in all tissues equally.47 Similar to the observations in humans, long-term treatment studies VLCAD−/− mice demonstrated that triheptanoin was indeed able to supply enough energy at rest.47 In addition, the metabolic and morphologic trans-differentiation towards the glycolytic muscle fibres type II observed as progressive adaptive mechanism was not reversed by the supplementation with this compound.48 On the other hand, at the cardiac level, although triheptanoin was not able to prevent the impairment of cardiac function, it did not contribute to progression of cardiac dysfunction in dilated cardiomyopathy in contrast to the regular MCT, similar to data reported for FAOD patients.43,47,49 Moreover, long-term supplementation of triheptanoin induced de novo lipo-genesis and elongation of fatty acids leading to the alteration of the fatty acid profiles in several tissues characterised by a strong reduction of polyunsaturated fatty acids and the marked increase of monounsaturated species.50 This change was accompanied by the subsequent alteration of complex lipids from the plasma membrane of different tissues from VLCAD−/− mice and from fibroblasts from patients with different lc-FAOD (unpublished data). Because complex lipids are essential in the maintenance of plasma membrane integrity and function, we speculate that a change in of the plasma membrane would result in an alteration of cell signalling and homeostasis.51-53

Finally, use of triheptanoin has been proposed for the treatment of other metabolic myopathies.54

### 2.5 Triheptanoin: controversial applications

Triheptanoin has been unsuccessful in treatment of several other disorders. Although an initial report showed a good safety profile and a promising result for the glyco-gen storage disorder, adult polyglucosan body disease,55,56 subsequent long term treatment (6 months) failed to show benefit.57 Similarly, triheptanoin was not able to restore TCA cycle substrate balance and showed no positive effects on exercise capacity or oxidative
metabolism during exercise, in patients with McArdle disease, a disorder of muscle glycogenolysis.58

Use of triheptanoin for pyruvate carboxylase deficiency (PCD) has also been reported. Despite an improvement in biochemical parameters in treated patients and an increased concentration of plasma ketone bodies in a 6-year-old girl with PCD type B, no biochemical or clinical improvement could be observed in three other patients with a severe PCD form.59–61

Triheptanoin failed to improve paroxysmal episodes in patients with alternating hemiplegia of childhood related to ATP1A3 variants.37 The ability of triheptanoin to improve bioenergetics in other conditions33,36,56,60 but was ineffective in this disorder, supports that the hypothesis that Na+/K+ ATPase dysfunction rather than lack of energetic intermediates leads to impaired sodium-dependent brain glucose transportation in this condition.37

Studies in rats have demonstrated that pre-treatment with triheptanoin prior to middle cerebral artery occlusion protected against oxidative stress62 and no physiologic effect was observed. Rather, a continuous 72 hours infusion of triheptanoin initiated 1 hour after middle cerebral artery occlusion in rats neither altered stroke volume nor ameliorated neurological deficit.62

Finally, triheptanoin treatment has been suggested as a possible treatment fatty liver; however, it did not reduce hepatic lipid content in mice despite an increase in the hepatic capacity for fatty-acid oxidation.63 Similarly, it led to the development of hepatic steatosis in a mouse model of VLCAD deficiency,47 although older studies proposed a hepatoprotective effect in a dose-dependent manner.64 The relationship of these rodent studies to human disease is unclear due to differences in fatty acid oxidation between the two species.

3 | CONCLUSIONS

Triheptanoin can effectively supply acetyl-CoA and propionyl-CoA to replete the TCA cycle and improve bioenergetics in some inborn errors of energy metabolism such as FAOD, G1D and PCD. The range disorders for which it may show benefit remains to be seen, but may be restricted to those that directly impair TCA cycle homeostasis and thus are amenable to the anaplerotic effect of triheptanoin.

CONFLICT OF INTEREST

S.T. has received a grant and travel reimbursements by Vitaflo and Dr. Schär unrelated to this study. Z.W. declares that she has no conflict of interest.

AUTHOR CONTRIBUTIONS

Z.W. was involved in literature search and drafting of the manuscript. S.T. was involved in the conception and design, and revising of the manuscript.

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