Received: 12 August 2019 | Revised: 25 November 2019 | Accepted: 27 November 2019

DOI: 10.1002/jimd.12199

REVIEW ARTICLE

JIMD SSIEM WILEY

Therapeutic potential of triheptanoin in metabolic and neurodegenerative diseases

Zeinab Wehbe[1,2] | **Sara Tucci**[1]

[1]Laboratory of Clinical Biochemistry and Metabolism, Department of General Pediatrics and Adolescent Medicine, Faculty of Medicine, Medical Center—University of Freiburg, Freiburg, Germany

[2]Faculty of Biology, University of Freiburg, Freiburg, Germany

Correspondence
Sara Tucci, Department of General Pediatrics and Adolescent Medicine, Laboratory of Clinical Biochemistry and Metabolism, Medical Center—University of Freiburg, Faculty of Medicine, Mathildenstrasse 1, D-79106 Freiburg, Germany.
Email: sara.tucci@uniklinik-freiburg.de

Communicating Editor: Jerry Vockley

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.[1] After cleavage by intestinal lipases heptanoate is absorbed by the gastrointestinal tract and metabolised predominantly in the liver.[2,3] 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.[4] Most of the circulating C8 fatty acids reach the liver where they can be directly metabolised.[4] 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 which can be further converted to succinyl-CoA, an anaplerotic substrate for the citric acid or tricarboxylic acid cycle (TCA)[5] and a substrate for complex II of the respiratory chain, thereby supporting mitochondrial energy production.[6] The anaplerotic effect of propionyl-CoA also indirectly supports gluconeogenesis through increased ATP generation.[3,7] 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).[8] Once released into the blood stream they cross the blood brain barrier and may be used as substrate for energy production in the absence of sufficient glucose.[2] Heptanoate in peripheral tissues is converted to acetyl-CoA and propionyl-CoA via 3-oxoacid-CoA supplying the tissues with the required energy.[2]

Triheptanoin is considered a strong anaplerotic substrate, replenishing the TCA cycle C4/C5 intermediate pool when deficient.[9] 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.[3] In fact, activation of AMPK signalling cascade due to reduced TCA intermediates leads to the activation of catabolic pathways, a process that is accompanied by a decline in ATP production and the deactivation of biosynthetic ATP consuming pathways.[3] In contrast, activation of the mTOR signalling pathway induces anabolic processes (Figure 1). Moreover, ATP promoted via TCA activity is also able to inhibit glutamate release, protecting tissue from ischaemic stroke in mice.[6] On the other hand, loss of ATP inhibits the Na,K-ATPase, increasing intracellular sodium resorption and activating the release of glutamate and the concomitant depletion of α-ketoglutarate, a low energy state that favours ischaemic strokes[6] (Figure 2).

Very recent studies in drosophila models of mitochondrial encephalopathy and glycolytic enzymopathy have shown that supplementation of triheptanoin mimics the success of the ketogenic diet even in the presence of standard carbohydrate levels due to its anaplerotic

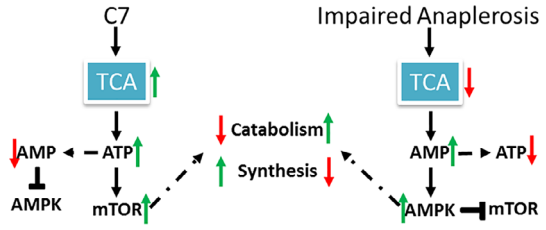

FIGURE 1 Schematic representation of the activation of AMPK and mTOR signalling by nutrients modified from Roe and Mochel.[3] Heptanoate and anaplerotic reactions supply the citric acid cycle (TCA) with the required and additional substrates. This process activates mTOR signalling with the subsequence 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

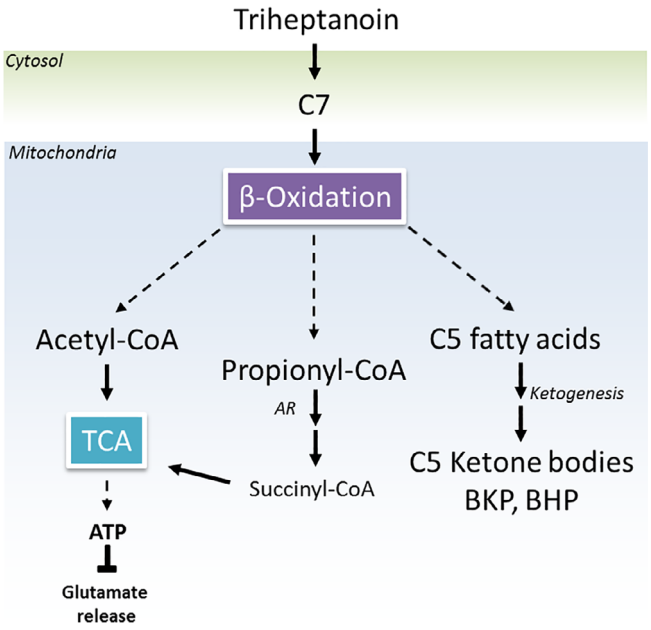

FIGURE 2 Schematic representation of the metabolism of triheptanoin. When heptanoic acid enters the mitochondria, it may undergo either one or two cycles of β-oxidation. In the first case, acetyl-CoA can serve as substrate for the TCA cycle and the C5 fatty acids can be used for the biosynthesis of C5 ketone bodies which are neuroprotective. The generated ATP can also inhibit the release of glutamate contributing to the prevention of ischaemic strokes. On the other hand, after two cycles of β-oxidation the generated two acetyl-CoA units can enter the either 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; $NADH/FADH_2$, nicotinamide adenine dinucleotide/flavin adenine dinucleotide; TCA, citric acid cycle

effect.[10] Moreover, triheptanoin does not appear to alter glucose metabolism in the healthy brain.[11] Of note, the mechanism of action of triheptanoin depends on the modality of administration. Studies in rats have shown that infusion as triglyceride emulsion not only activates plasma lipoprotein lipase (which hydrolyses the infused triglyceride), but also stimulates lipolysis and the release of long-chain fatty acid release from adipose tissue even though the re-esterification rate of these fatty acids is 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 States[12] 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 untreatable epilepsy.[17] However, most of patients can be treated either medications that aim to decrease the neuronal excitability,[13,14] or by surgery, by neuromodulation 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] Futhermore, enrichment studies with [U-$^{13}C_6$]-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 epileptic 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, Adenyeguh 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 ongoing[41] (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 lipogenesis 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 glycogen 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 conditions[33,36,56,60] 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 pretreatment with triheptanoin prior to middle cerebral artery occlusion protected against oxidative stress[62] 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.

REFERENCES

1. Pascual JM, Liu P, Mao D, et al. Triheptanoin for glucose transporter type I deficiency (G1D): modulation of human ictogenesis, cerebral metabolic rate, and cognitive indices by a food supplement. *JAMA Neurol*. 2014;71(10):1255-1265.
2. Gu L, Zhang GF, Kombu RS, et al. Parenteral and enteral metabolism of anaplerotic triheptanoin in normal rats. II. Effects on lipolysis, glucose production, and liver acyl-CoA profile. *Am J Physiol Endocrinol Metab*. 2010;298(2):E362-E371.
3. Roe CR, Mochel F. Anaplerotic diet therapy in inherited metabolic disease: therapeutic potential. *J Inherit Metab Dis*. 2006;29 (2–3):332-340.
4. Lemarie F, Beauchamp E, Legrand P, Rioux V. Revisiting the metabolism and physiological functions of caprylic acid (C8:0) with special focus on ghrelin octanoylation. *Biochimie*. 2016; 120:40-48.
5. Borges K, Sonnewald U. Triheptanoin—a medium chain triglyceride with odd chain fatty acids: a new anaplerotic anticonvulsant treatment? *Epilepsy Res*. 2012;100(3):239-244.
6. Schwarzkopf TM, Koch K, Klein J. Reduced severity of ischemic stroke and improvement of mitochondrial function after dietary treatment with the anaplerotic substance triheptanoin. *Neuroscience*. 2015;300:201-209.
7. Adanyeguh IM, Rinaldi D, Henry PG, et al. Triheptanoin improves brain energy metabolism in patients with Huntington disease. *Neurology*. 2015;84(5):490-495.
8. Mochel F. Triheptanoin for the treatment of brain energy deficit: a 14-year experience. *J Neurosci Res*. 2017;95(11):2236-2243.
9. Brunengraber H, Roe CR. Anaplerotic molecules: current and future. *J Inherit Metab Dis*. 2006;29(2–3):327-331.
10. Fogle KJ, Smith AR, Satterfield SL, et al. Ketogenic and anaplerotic dietary modifications ameliorate seizure activity in drosophila models of mitochondrial encephalomyopathy and glycolytic enzymopathy. *Mol Genet Metab*. 2019;126(4):439-447.
11. McDonald TS, Tan KN, Hodson MP, Borges K. Alterations of hippocampal glucose metabolism by even versus uneven medium chain triglycerides. *J Cereb Blood Flow Metab*. 2014;34 (1):153-160.
12. Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the "common" neurologic disorders? *Neurology*. 2007;68(5):326-337.
13. Hadera MG, McDonald T, Smeland OB, et al. Modification of astrocyte metabolism as an approach to the treatment of epilepsy: triheptanoin and acetyl-L-carnitine. *Neurochem Res*. 2016;41(1–2):86-95.
14. Devinsky O, Vezzani A, O'Brien TJ, et al. Epilepsy. *Nat Rev Dis Primers*. 2018;4:18024.
15. Weber YG, Biskup S, Helbig KL, Von Spiczak S, Lerche H. The role of genetic testing in epilepsy diagnosis and management. *Expert Rev Mol Diagn*. 2017;17(8):739-750.
16. Blume WT. Focal and generalized: both here and there. *Epilepsy Curr*. 2010;10(5):115-117.
17. Perez-Perez D, Frias-Soria CL, Rocha L. Drug-resistant epilepsy: from multiple hypotheses to an integral explanation

using preclinical resources. *Epilepsy Behav*. 2019;106430. https://doi.org/10.1016/j.yebeh.2019.07.031
18. McDonald T, Puchowicz M, Borges K. Impairments in oxidative glucose metabolism in epilepsy and metabolic treatments thereof. *Front Cell Neurosci*. 2018;12:274.
19. Willis S, Stoll J, Sweetman L, Borges K. Anticonvulsant effects of a triheptanoin diet in two mouse chronic seizure models. *Neurobiol Dis*. 2010;40(3):565-572.
20. Borges K, Kaul N, Germaine J, Kwan P, O'Brien TJ. Randomized trial of add-on triheptanoin vs medium chain triglycerides in adults with refractory epilepsy. *Epilepsia Open*. 2019;4(1):153-163.
21. Marin-Valencia I, Hooshyar MA, Pichumani K, Sherry AD, Malloy CR. The ratio of acetate-to-glucose oxidation in astrocytes from a single 13C NMR spectrum of cerebral cortex. *J Neurochem*. 2015;132(1):99-109.
22. McDonald T, Hodson MP, Bederman I, Puchowicz M, Borges K. Triheptanoin alters [U-(13)C6]-glucose incorporation into glycolytic intermediates and increases TCA cycling by normalizing the activities of pyruvate dehydrogenase and oxoglutarate dehydrogenase in a chronic epilepsy mouse model. *J Cerebr Blood Flow Metab*. 2019:1-14. https://doi.org/10.1177/0271678X19837380
23. Tan KN, Simmons D, Carrasco-Pozo C, Borges K. Triheptanoin protects against status epilepticus-induced hippocampal mitochondrial dysfunctions, oxidative stress and neuronal degeneration. *J Neurochem*. 2018b;144(4):431-442.
24. Kim TH, Borges K, Petrou S, Reid CA. Triheptanoin reduces seizure susceptibility in a syndrome-specific mouse model of generalized epilepsy. *Epilepsy Res*. 2013;103(1):101-105.
25. Thomas NK, Willis S, Sweetman L, Borges K. Triheptanoin in acute mouse seizure models. *Epilepsy Res*. 2012;99(3):312-317.
26. Calvert S, Barwick K, Par M, Ni Tan K, Borges K. A pilot study of add-on oral triheptanoin treatment for children with medically refractory epilepsy. *Eur J Paediatr Neurol*. 2018;22(6):1074-1080.
27. Park MJ, Aja S, Li Q, et al. Anaplerotic triheptanoin diet enhances mitochondrial substrate use to remodel the metabolome and improve lifespan, motor function, and sociability in MeCP2-null mice. *PLoS One*. 2014;9(10):e109527.
28. Tefera TW, Tan KN, McDonald TS, Borges K. Alternative fuels in epilepsy and amyotrophic lateral sclerosis. *Neurochem Res*. 2017;42(6):1610-1620.
29. Tefera TW, Wong Y, Barkl-Luke ME, et al. Triheptanoin protects motor neurons and delays the onset of motor symptoms in a mouse model of amyotrophic lateral sclerosis. *PLoS One*. 2016;11(8):e0161816.
30. Aso E, Semakova J, Joda L, et al. Triheptanoin supplementation to ketogenic diet curbs cognitive impairment in APP/PS1 mice used as a model of familial Alzheimer's disease. *Curr Alzheimer Res*. 2013;10(3):290-297.
31. Mochel F, Duteil S, Marelli C, et al. Dietary anaplerotic therapy improves peripheral tissue energy metabolism in patients with Huntington's disease. *Eur J Hum Genet*. 2010;18(9):1057-1060.
32. Francis JS, Markov V, Leone P. Dietary triheptanoin rescues oligodendrocyte loss, dysmyelination and motor function in the nur7 mouse model of Canavan disease. *J Inherit Metab Dis*. 2014;37(3):369-381.
33. Mochel F, Hainque E, Gras D, et al. Triheptanoin dramatically reduces paroxysmal motor disorder in patients with GLUT1 deficiency. *J Neurol Neurosurg Psychiatry*. 2016;87(5):550-553.
34. Marin-Valencia I, Good LB, Ma Q, et al. Glut1 deficiency (G1D): epilepsy and metabolic dysfunction in a mouse model of the most common human phenotype. *Neurobiol Dis*. 2012;48(1):92-101.
35. Marin-Valencia I, Good LB, Ma Q, Malloy CR, Pascual JM. Heptanoate as a neural fuel: energetic and neurotransmitter precursors in normal and glucose transporter I-deficient (G1D) brain. *J Cereb Blood Flow Metab*. 2013;33(2):175-182.
36. Gras D, Roze E, Caillet S, et al. GLUT1 deficiency syndrome: an update. *Rev Neurol*. 2014;170(2):91-99.
37. Hainque E, Caillet S, Leroy S, et al. A randomized, controlled, double-blind, crossover trial of triheptanoin in alternating hemiplegia of childhood. *Orphanet J Rare Dis*. 2017;12(1):160.
38. Klepper J. GLUT1 deficiency syndrome in clinical practice. *Epilepsy Res*. 2012;100(3):272-277.
39. Roe CR, Brunengraber H. Anaplerotic treatment of long-chain fat oxidation disorders with triheptanoin: review of 15 years experience. *Mol Genet Metab*. 2015;116(4):260-268.
40. Roe CR, Sweetman L, Roe DS, David F, Brunengraber H. Treatment of cardiomyopathy and rhabdomyolysis in long-chain fat oxidation disorders using an anaplerotic odd-chain triglyceride. *J Clin Invest*. 2002;110(2):259-269.
41. Leslie ND, Valencia CA, Strauss AW, Zhang K. Very long-chain acyl-coenzyme A dehydrogenase deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews®*. Seattle, WA: University of Washington; 1993.
42. Vockley J, Burton B, Berry GT, et al. UX007 for the treatment of long chain-fatty acid oxidation disorders: safety and efficacy in children and adults following 24 weeks of treatment. *Mol Genet Metab*. 2017;120(4):370-377.
43. Gillingham MB, Heitner SB, Martin J, et al. Triheptanoin versus trioctanoin for long-chain fatty acid oxidation disorders: a double blinded, randomized controlled trial. *J Inherit Metab Dis*. 2017;40(6):831-843.
44. Vockley J, Charrow J, Ganesh J, et al. Triheptanoin treatment in patients with pediatric cardiomyopathy associated with long chain-fatty acid oxidation disorders. *Mol Genet Metab*. 2016;119(3):223-231.
45. Mahapatra S, Ananth A, Baugh N, Damian M, Enns GM. Triheptanoin: a rescue therapy for cardiogenic shock in carnitine-acylcarnitine translocase deficiency. *JIMD Rep*. 2018;39:19-23.
46. Roe CR, Yang BZ, Brunengraber H, Roe DS, Wallace M, Garritson BK. Carnitine palmitoyltransferase II deficiency: successful anaplerotic diet therapy. *Neurology*. 2008;71(4):260-264.
47. Tucci S, Floegel U, Beermann F, Behringer S, Spiekerkoetter U. Triheptanoin: long-term effects in the very long-chain acyl-CoA dehydrogenase (VLCAD−/−)-deficient mouse. *J Lipid Res*. 2016;58(1):196-207.
48. Tucci S, Mingirulli N, Wehbe Z, Dumit VI, Kirschner J, Spiekerkoetter U. Mitochondrial fatty acid biosynthesis and muscle fiber plasticity in very long-chain acyl-CoA dehydrogenase-deficient mice. *FEBS Lett*. 2018;592(2):219-232.
49. Tucci S. Very long-chain acyl-CoA dehydrogenase (VLCAD-) deficiency-studies on treatment effects and long-term outcomes in mouse models. *J Inherit Metab Dis*. 2017;40(3):317-323.
50. Tucci S, Behringer S, Spiekerkoetter U. De novo fatty acid biosynthesis and elongation in very long-chain acyl-CoA dehydrogenase-(VLCAD) deficient mice supplemented with odd or even medium-chain fatty acids. *FEBS J*. 2015;282:4242-4253.

51. de Kroon AI, Rijken PJ, De Smet CH. Checks and balances in membrane phospholipid class and acyl chain homeostasis, the yeast perspective. *Prog Lipid Res*. 2013;52(4):374-394.
52. Sunshine H, Iruela-Arispe ML. Membrane lipids and cell signaling. *Curr Opin Lipidol*. 2017;28(5):408-413.
53. Zwaal RF, Comfurius P, van Deenen LL. Membrane asymmetry and blood coagulation. *Nature*. 1977;268(5618):358-360.
54. Orngreen MC, Vissing J. Treatment opportunities in patients with metabolic myopathies. *Curr Treat Options Neurol*. 2017;19(11):37.
55. Alvarez R, Casas J, Lopez DJ, et al. Triacylglycerol mimetics regulate membrane interactions of glycogen branching enzyme: implications for therapy. *J Lipid Res*. 2017;58(8):1598-1612.
56. Roe CR, Bottiglieri T, Wallace M, Arning E, Martin A. Adult polyglucosan body disease (APBD): anaplerotic diet therapy (triheptanoin) and demonstration of defective methylation pathways. *Mol Genet Metab*. 2010;101(2–3):246-252.
57. Schiffmann R, Wallace ME, Rinaldi D, et al. A double-blind, placebo-controlled trial of triheptanoin in adult polyglucosan body disease and open-label, long-term outcome. *J Inherit Metab Dis*. 2018;41(5):877-883.
58. Madsen KL, Laforet P, Buch AE, et al. No effect of triheptanoin on exercise performance in McArdle disease. *Ann Clin Transl Neurol*. 2019;6:1949-1960.
59. Breen C, White FJ, Scott CA, et al. Unsuccessful treatment of severe pyruvate carboxylase deficiency with triheptanoin. *Eur J Pediatr*. 2014;173(3):361-366.
60. Mochel F, DeLonlay P, Touati G, et al. Pyruvate carboxylase deficiency: clinical and biochemical response to anaplerotic diet therapy. *Mol Genet Metab*. 2005;84(4):305-312.
61. Wang D, De Vivo D. Pyruvate carboxylase deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews®*. Seattle, WA: University of Washington; 1993.
62. Tan KN, Hood R, Warren K, et al. Heptanoate is neuroprotective in vitro but triheptanoin post-treatment did not protect against middle cerebral artery occlusion in rats. *Neurosci Lett*. 2018a;683:207-214.
63. Comhair TM, Garcia Caraballo SC, Dejong CH, Lamers WH, Koehler SE. The odd-carbon medium-chain fatty triglyceride triheptanoin does not reduce hepatic steatosis. *Clin Nutr*. 2017;36(1):229-237.
64. Silva MA, Ataide Tda R, Oliveira SL, et al. Hepatoprotective effect of diheptanoin and tritreptanoin chronic consumption against steatosis in rats. *Arq Bras Endocrinol Metabol*. 2008;52(7):1145-1155.

How to cite this article: Wehbe Z, Tucci S. Therapeutic potential of triheptanoin in metabolic and neurodegenerative diseases. *J Inherit Metab Dis*. 2020;43:385–391. https://doi.org/10.1002/jimd.12199