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Triheptanoin—A medium chain triglyceride with odd chain fatty acids: A new anaplerotic anticonvulsant treatment?

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Summary The triglyceride of heptanoate (C7 fatty acid), triheptanoin, is a tasteless oil used to treat rare metabolic disorders in USA and France. Heptanoate is metabolized by β-oxidation to provide propionyl-CoA, which after carboxylation can produce succinyl-CoA, resulting in anaplerosis — the refilling of the tricarboxylic acid cycle. Heptanoate is also metabolized by the liver to the C5 ketones, β-ketopentanoate and/or β-hydroxypentanoate, which are released into the blood and thought to enter the brain via monocarboxylate transporters. Oral triheptanoin has recently been discovered to be reproducibly anticonvulsant in acute and chronic mouse seizures models. However, current knowledge on alterations of brain metabolism after triheptanoin administration and anaplerosis via propionyl-CoA carboxylation in the brain is limited. This review outlines triheptanoin's unique anticonvulsant profile and its clinical potential for the treatment of medically refractory epilepsy. Anaplerosis as a therapeutic approach for the treatment of epilepsy is discussed. More research is needed to elucidate the anticonvulsant mechanism of triheptanoin and to reveal its clinical potential for the treatment of epilepsy and other disorders of the brain.

Introduction

Dysfunction of metabolic processes appears to play a major role in conditions that include seizures as well as certain forms of epilepsy. This notion is corroborated by two main types of observations. (1) Mutations in genes that are involved in energy and/or ATP metabolism are associated with epileptic seizures, e.g. glucose transporter 1 (GLUT1) deficiency, but also mutations of mitochondrial constituents. (2) Several manipulations of metabolic pathways are efficacious in rodent seizure models and/or epilepsy patients. This includes the ketogenic diet (as discussed in this supplement), fructose-1,6-bisphosphate in rat epilepsy models (Lian et al., 2007, 2008) and 2-deoxy-D-glucose in certain rat and mouse models (Garriga-Canut et al., 2006; Stafstrom et al., 2009). Triheptanoin is a medium chain triglyceride

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Table 1 Comparison of the anticonvulsant properties of triheptanoin in mice compared to other treatments for epilepsy.

	Triheptanoin	Ketogenic diet	PHT	VPA	CBZ	LEV
MEST	+[1]	−[3]	+[6]	+[6]	+[6]	−[11]
PTZ	−[2]	−[3,4]	−[6]	+[6]	−[6]	−[11]
6 Hz	−[1]	+[3,4,5]	+[7]	+[7]	±[7]	+[7]
PTZ in PILO-SE rodents	+[2]	nd	−[8]	−[8]	nd	nd
Corneal kindling						
A. Delay in kindling progression	+[2]	nd	nd	nd	nd	+[12]
B.Protection against fully kindled seizures	(−)[2]*	nd	+ [9,10]	+[9]	+[9]	+[9]

Efficacy in mouse seizure models is noted as minus (−) or plus (+) or some (±). Exceptions are the PTZ model which was performed in rats for the testing of PHT and VPA.
Abbreviations: KD — ketogenic diet, PHT — phenytoin, VPA — valproate, CBZ — carbamazepine, LEV — levetiracetam. *Note that only one experiment was performed.
References: [1]Thomas et al. (submitted), [2]Willis et al. (2010), [3]Hartman et al. (2007), [4]Hartman et al. (2008), [5]Samala et al. (2008), [6]White et al. (2002), [7]Barton et al. (2001), [8]data from rats, Blanco et al. (2009), [9]Rowley and White (2010), [10]Potschka and Löscher (1999), [11]Klitgaard et al. (1998), [12]Matagne and Klitgaard (1998).

containing three odd chain fatty acid heptanoate molecules. It is clear tasteless oil, which can easily be added to any diet. Roe, Brunengraber and colleagues discovered triheptanoin as an oral anaplerotic treatment for metabolic disorders (Roe et al., 2002; Brunengraber and Roe, 2006; Roe and Mochel, 2006). This sparked interest in its potential for the treatment of epilepsy, resulting in the recent finding that triheptanoin feeding is anticonvulsant in three mouse epilepsy models. In this review we discuss the current knowledge of triheptanoin in terms of its anticonvulsant and metabolic effects and its clinical potential in comparison to the ketogenic diet.

Triheptanoin's anticonvulsant profile

At the time of writing this article, triheptanoin feeding as an anticonvulsant treatment in rodents has only been evaluated by two laboratories. In 2008 it was described that short term feeding of triheptanoin within a context of a ketogenic diet inhibited cortical spreading depression in young rats (de Almeida Rabello Oliveira et al., 2008). The Borges' laboratory investigated the effect of oral triheptanoin in the context of a more regular ''low fat'' diet, a composition largely based on the clinical studies by Roe. Given that in clinical studies up to 35% of the daily caloric intake is provided in the form of triheptanoin, standard rodent chow was modified accordingly to include 170 ml of triheptanoin per kg rodent diet (Willis et al., 2010). Other components of regular rodent chows, such as 150 g sucrose and some of the complex carbohydrates and fats were omitted to accommodate the amount triheptanoin added. Fed to mice, the dietary intake of protein, antioxidants, vitamins and minerals was similar between standard vs. triheptanoin diet. In metabolic cages, a 30 g mouse consumed on average, 5 g of triheptanoin-containing diet per day, corresponding to a dose of 0.85 ± 0.2 g triheptanoin per day (average and standard error of the mean for 4 experiments). In our initial experiments up to two weeks of triheptanoin feeding did not induce reproducible anticonvulsant activity in acute mouse seizure models, such as the fluorothyl, 6 Hz and pentylenetetrazole (PTZ) (i.v.) tests (Thomas et al., unpublished). In contrast, we found reproducible anticonvulsant effects after $\geq$three weeks of feeding in one acute and two chronic mouse seizure models in CD1 and CF1 mice, respectively. In the maximal electroshock threshold test in CD1 mice, we recently found a small but reproducible increase of the critical current at which 50% of mice seize (Willis et al., unpublished). We are currently investigating the minimum triheptanoin feeding amount and time required for this effect. In the corneal kindling model we found a reproducible delay in the kindling process in CF1 mice. This effect is similar to results found with low doses of levetiracetam in the same model (Matagne et al., 2008) and valproate, phenobarbital and lacosamide in the rat amygdala kindling model (Brandt et al., 2006; Silver et al., 1991). Lastly, we used a second hit pentylenetetrazole (PTZ, i.v.) test in CF1 mice that were subjected to pilocarpine-induced status epilepticus (PILO-SE). Mice and rats that experience PILO-SE develop spontaneous seizures (Turski et al., 1984, 1983) and increased sensitivity to PTZ. In our hands, there was no evidence of spontaneous seizures or increased seizure threshold in mice that did not develop SE (no SE mice, Willis et al., 2010). In two experiments, triheptanoin reproducibly increased the PTZ seizure threshold in CF1 mice that had experienced PILO-SE. The fact that there was no effect of triheptanoin in the PTZ test in PILO-no SE mice suggests that triheptanoin feeding is particularly effective in mice with spontaneous recurrent seizures.

Table 1 summarizes and compares the anticonvulsant profiles of triheptanoin and some of the most commonly used antiepileptic drugs and the ketogenic diet. The table needs to be interpreted with caution, because not all the specific conditions of animal epilepsy models used could be taken into account. For example, PTZ models vary between different laboratories and anticonvulsant efficacy of certain drugs is dependent on the PTZ administration route and the rodent used (Löscher et al., 1991). Also, data on the anticonvulsant effects of ketogenic diets in animal models can vary across laboratories (Susan Masino, Adam Hartman, personal communication) (Hartman et al., 2007, 2008; Samala et al., 2008; Borges, 2008). To our knowledge, antiepileptic