Molecular Genetics and Metabolism 145 (2025) 109177

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Letter to the Editor

The origin of abnormal organic acids in HMG-CoA synthase deficiency

ARTICLE INFO

Keywords:
Ketogenesis defect
HMG-CoA synthase
Organic aciduria

Dear Sir,

In a recent article published in *Mol Genet Metab*, Decru et al. review a large cohort of patients with HMGCS2 deficiency [1]. The authors highlight the diagnostic value of 4-hydroxy-6-methyl-2-pyrone (4H6MP) and other abnormal hexanoic acid derivatives, but they do not comment on how they are formed. Since the first publication of organic aciduria in HMGCS2 deficiency, it is commonly assumed that they result from ω and ω-1 oxidation of hexanoyl-CoA [2]. However, this hypothesis does not fit well with the presence of 3,5-dihydroxy- and/or keto-hexanoic acid derivatives.

We propose that these metabolites derive from a beta-ketothiolase-catalysed reaction of acetyl-CoA with acetoacetyl-CoA, L-3-hydroxybutyryl-CoA or crotonyl-CoA. These four metabolites likely accumulate in mitochondria due to the metabolic block (Fig. 1). Lactonization of 3,5-diketohexanoyl-CoA, presumably initiated by the formation of a resonance-stabilized enolate, would lead to the 4-hydroxy-6-methyl-2-pyrone **(1)**. Furthermore, the 3-keto function of the three 'abnormal' products made by the beta-ketothiolase would be reduced by L-3-hydroxyacylCoA dehydrogenase to yield L-3-hydroxy-acyl-CoAs, which, after thiolysis or lactonization, would form **(2), (3), (4), (5)** and **(7).** Of note, mitochondria contain also a NAD-linked D-3-hydroxyacyl-CoA dehydrogenase associated to 3-oxoacyl-ACP reductase [3] and potentially forming the related D-3-hydroxy-acyl-CoAs. This could explain that two separable forms of **(4)** and **(5)** are observed [2]. They would correspond to L-3,L-5-dihydroxy- and D-3,L-5-dihydroxy- derivatives of hexanoate and its lactone. Finally, **(6)** would result from dehydration of 3,5-dihydroxy-hexanoyl-CoA by an enoyl-CoA hydratase followed by thiolysis. The side reactions (enzyme promiscuity) of well-known enzymes that we assume to participate in this pathway are not unreasonable, considering that the formation of the abnormal products represent minor pathways compared to beta-oxidation.

Although our hypothesis remains speculative and should be confirmed by further experimental data, it has the advantage of providing a straightforward explanation for Pitt's metabolites. In addition, it explains why such metabolites are not prevalently observed in other fatty acid β-oxidation defects, especially MCAD deficiency where hexanoyl-CoA accumulates, but acetoacetyl-CoA does not.

External funding

None.

CRediT authorship contribution statement

F.-G. Debray: Writing – original draft, Conceptualization. **E. Van Schaftingen:** Writing – review & editing, Conceptualization.

Declaration of competing interest

None.

Data availability

No data was used for the research described in the article.

https://doi.org/10.1016/j.ymgme.2025.109177
Received 30 April 2025; Received in revised form 12 June 2025; Accepted 12 June 2025
Available online 13 June 2025

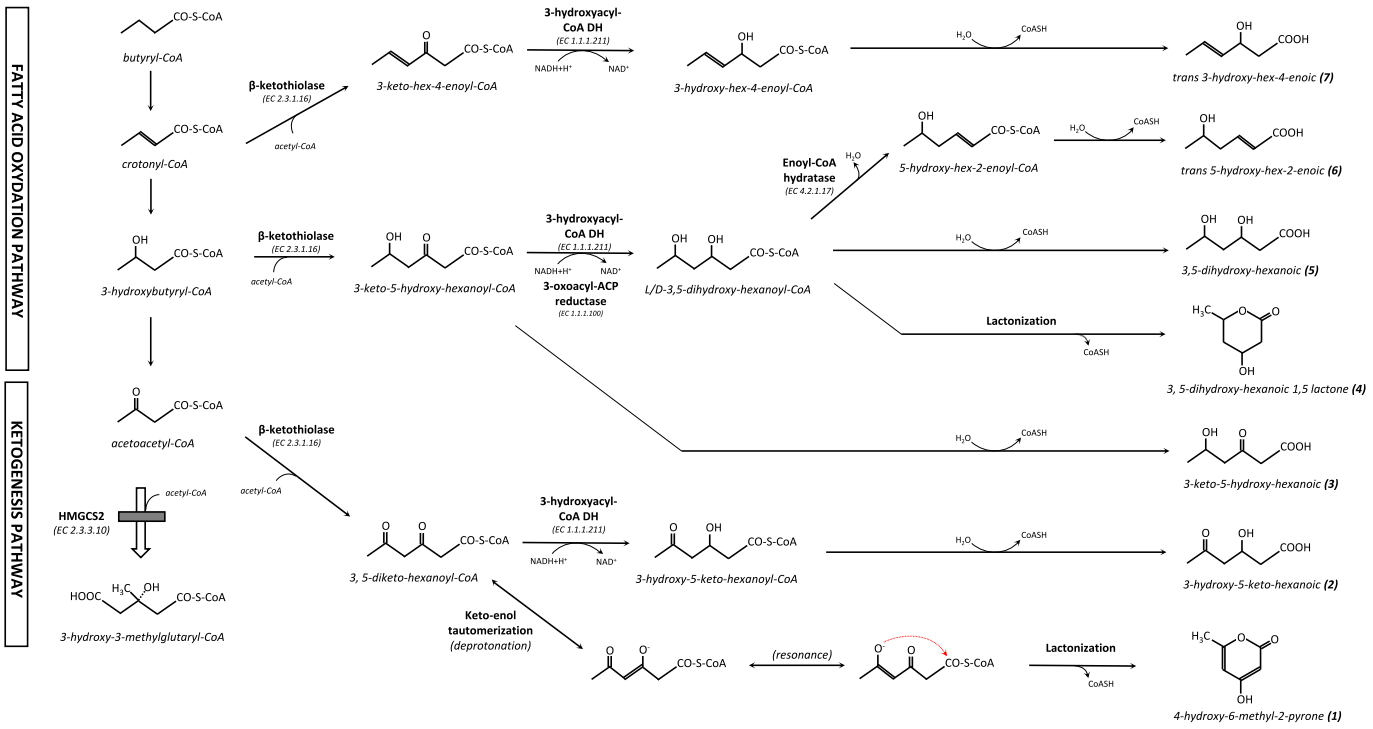

Fig. 1. Suggested pathway for abnormal organic aciduria in HMGCS2 deficiency

References

[1] B. Decru, M. Lys, K. Truijens, et al., Mitochondrial HMG-CoA synthase deficiency, Mol. Genet. Metab. 144 (2025) 109007.
[2] J.J. Pitt, H. Peters, A. Boneh, et al., Mitochondrial 3-hydroxy-3methylglutaryl-CoA synthase deficiency : urinary organic acid profiles and expanded spectrum of mutations, J. Inherit. Metab. Dis. 38 (3) (2015) 459–466.
[3] R. Venkatesan, S.K. Sah-Teli, L.O. Awonyi, et al., Insights into mitochondrial fatty acid synthesis from the structure of heterotetrameric 3-ketoacyl-ACP reductase/3R-hydroxyacyl-CoA dehydrogenase, Nat. Commun. 5 (2014) 4805.

F.-G. Debray[a,*], E. Van Schaftingen[b]
[a] *Department of Human Genetics, CHU & Liège University, Liège, Belgium*
[b] *De Duve Institute, Université Catholique de Louvain (UCLouvain), Brussels, Belgium*

[*] Corresponding author.
E-mail address: fg.debray@chuliege.be (F.-G. Debray).