In silico evidence for gluconeogenesis from fatty acids in humans

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Abstract

The question whether even-chain fatty acids can be converted into glucose in humans at metabolic steady state has been a topic of intense debate in biochemistry in the early 20th century. With the discovery of the glyoxylate shunt in several organisms and the finding that the corresponding enzymes appear not to be present in humans, the conclusion had been that this conversion would not be possible in humans [1]. By analysing the core of central metabolism, this assertion has been confirmed by elementary-modes analysis [2]. Intuitively, this can be explained in that two carbons enter the TCA cycle from acetyl-CoA and two (other) carbons are lost in the form of CO_2, so that no carbons are left for gluconeogenesis.

However, several observations have not been in agreement with this biochemical dogma. How can hibernating animals survive mainly on their fat reserves although some tissues such as the brain require glucose? How could inuit and other native people of the arctic regions live on their traditional, practically carbohydrate-free diet? Previous works on this issue did not take into account the full breadth of metabolic functions in humans and higher animals. On an anecdotal basis, some ideas about possible gluconeogenic routes starting from fatty acids have been put forward earlier [3].

By a comprehensive, systematic in silico analysis, we investigated whether there do exist routes for gluconeogenesis from fatty acids in a genome-scale model of human metabolism [4]. We used the genome-scale model established by Duarte et al. [5] and the method of elementary flux patterns [6]. Despite the long-held belief in biochemistry that such a conversion would not be possible, we detected several routes on which gluconeogenesis

from fatty acids is feasible in humans [4]. Analyzing experimental data from situations in which gluconeogenesis is particularly active, we could confirm that these routes appear to contribute, albeit to a limited extent. All these conversion routes run via acetone and are in agreement with earlier speculations [3]. Since our analysis is comprehensive, it also shows that there are no other feasible routes than the detected ones.

Our study is likely to have implications for nutritional sciences and sports physiology. For example, in prolonged exercise such as marathon races, the depletion of glucose is an issue. Moreover, our results underline the usefulness of whole-cell models because such networks allow for a comprehensive identification of pathways on which a given substrate can be transformed into a given product at steady state.

References

1. Weinman EO, Srisower EH, & Chaikoff IL (1957) Conversion of fatty acids to carbohydrate; application of isotopes to this problem and role of the Krebs cycle as a synthetic pathway. *Physiol. Rev.* 37, 252-272.

2. de Figueiredo LF, Schuster S, Kaleta C, Fell DA (2009) Can sugars be produced from fatty acids? A test case for pathway analysis tools. *Bioinformatics* 25, 152-158.

3. Argilés JM (1986) Has acetone a role in the conversion of fat to carbohydrates in mammals? *Trends Biochem. Sci.* 11, 61-63.

4. Kaleta C, de Figueiredo LF, Werner S, Guthke R, Ristow M, Schuster S (2011) In silico evidence for gluconeogenesis from fatty acids in humans. *PLoS Comp. Biol.* 7, e1002116

5. Duarte NC, Becker SA, Jamshidi N, Thiele I, Mo ML, et al. (2007) Global reconstruction of the human metabolic network based on genomic and bibliomic data. *Proc. Natl. Acad. Sci. U.S.A.* 104, 1777-1782.

6. Kaleta C, de Figueiredo LF, & Schuster S (2009) Can the whole be less than the sum of its parts? Pathway Analysis in genome-scale metabolic networks using elementary flux patterns. *Genome Res.* 19, 1872-1883.