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OCT1 in hepatic steatosis and thiamine disposition

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The human organic cation transporter, OCT1 (*SLC22A1*), a member of the SLC22 family, was first cloned in 1997.[1] Since then OCT1 has been characterized as a major drug transporter in the liver, transporting important pharmacologic agents including the anti-diabetic drug, metformin and the anti-cancer drug, oxaliplatin. Genetic polymorphisms of OCT1 have been associated with variation in the disposition and response to drugs such as codeine[2] and metformin,[3] and with variation in serum levels of various metabolites (http://www.genome.gov/gwastudies/). Initial studies in *Oct1*$^{-/-}$ mice showed that deletion of *Oct1* resulted in no observable physiologic changes.

Our recent report contradicts these initial findings, and suggests that OCT1 has an important physiologic role beyond xenobiotic disposition, in mammals. Notably, we found that OCT1 is a high capacity thiamine transporter, and as such plays an important role in carbohydrate and lipid metabolism in hepatocytes.[3] Our findings were based on integrated experimental approaches using cells, tissues, mouse models, metabolomic methods, and various molecular approaches to characterize the endogenous role of OCT1 including its principal substrate.[3]

A key observation, that *Oct1* deficiency alleviated hepatic steatosis in leptin deficient mice, inspired our further investigations. Our discovery (using metabolomic and isotopic uptake methods) that thiamine is the principal endogenous substrate of OCT1 provided the rationale for the reduced hepatic steatosis in the *Oct1*$^{-/-}$ mice. In particular, the thiamine derivative, thiamine pyrophosphate (TPP), is crucial for converting pyruvate to acetyl-CoA for glucose oxidative phosphorylation (ATP production) and fatty acid synthesis. The "short fall" in glycolytic energy production caused by OCT1 disruption in the knockout mice triggered increases in fatty acid oxidation to compensate for the energy requirement of the cell (**Fig. 1**). The dual effects caused by OCT1 deficiency (reduced glucose oxidation and increased β-oxidation) modulated the energy flow in the hepatocytes.

Supporting the decreased glycolytic energy production, reductions in glucose oxidation rates, ATP levels and levels of key gluconeogenic enzymes, such as glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) (5) were observed in the livers of *Oct1* deficient mice. Further, OCT1 expression was predominantly restricted to the perivenous zone responsible for glycolysis and lipogenesis.[3,4] Finally, our re-discovery that thiamine deficiency in rodents results in reduced hepatic steatosis implicates thiamine deficiency in the liver as the potential cause of the reduced hepatic steatosis in the *Oct1* deficient mice.

Beyond an understanding of basic physiology, our study has 3 critical implications. First, the findings suggest that there is a dose-response relationship for thiamine in terms of fat accumulation in the liver. The epidemic of beriberi that occurred in the early part of the 20th century was abated by thiamine supplementation in various products such as rice and bread. However our study raises an important point. Can thiamine supplementation be taken too far? Is too much thiamine a culprit for fatty liver disease? Clearly, the role of thiamine needs to be examined in light of the current epidemic in metabolic syndrome and diabetes. Second, our findings suggest that OCT1 represents an excellent target for the treatment of fatty liver disease and nonalcoholic steatohepatitis (NASH), an increasing health problem with limited therapeutic options.[5] Developing small molecules or monoclonal antibodies against OCT1 would open a new window for NASH treatment.

Finally, our study has important implications for the mechanisms of action of metformin, which is widely prescribed for the treatment of type 2 diabetes mellitus. How metformin acts has been the subject of numerous studies.[6,7] Our study suggests that in addition to transporting metformin, OCT1 may serve as a target for metformin. In particular, parallel effects of metformin and *Oct1* deficiency in mice were noted. For example, *Oct1* deficiency and administration of metformin both result in reduced hepatic steatosis, and increased phosphorylation of AMPK and ACC. Moreover, we observed that metformin competitively inhibited OCT1-mediated thiamine uptake in transfected cells. *In vivo, Oct1* deficiency resulted in substantially reduced intestinal and liver levels of thiamine; similarly, metformin treatment resulted in reduced intestinal and systemic plasma levels of thiamine and a trend toward reduced liver levels of thiamine. Modulation of thiamine levels by metformin (via OCT1 and perhaps other thiamine transporters) may be critically important in its beneficial effects on diabetes, hepatic steatosis, obesity and cancer.

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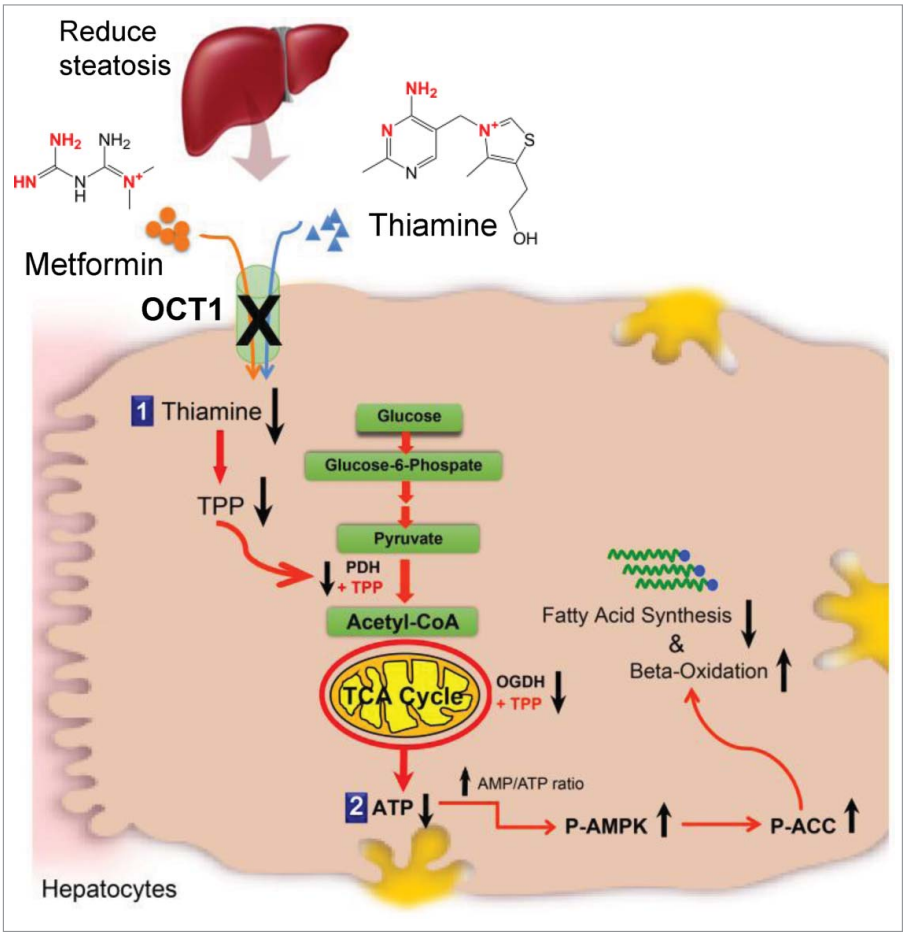

Figure 1. The physiological role of OCT1 in the liver. Thiamine enters hepatocytes through OCT1. Deletion or inhibition of OCT1 reduces thiamine and TPP levels [1] and hence reduces glucose oxidation and *de novo* lipogenesis. The reduced ATP from glucose [2] activates AMPK and increases ACC phosphorylation and hence increases β-oxidation and reduces fatty acid synthesis. Structurally similar to thiamine, metformin inhibits thiamine uptake and hence mimics the effect of OCT1 deficiency in the liver.

Collectively, the findings of our study present a compelling role for OCT1 in thiamine disposition, hepatic steatosis and energy production, and potentially in the mechanisms of metformin action (**Fig. 1**). However, in closing, several other points are worth mentioning. Firstly, exploration of the role of other endogenous substrates of OCT1, for example, serotonin, is needed. Secondly, studies of interactions between metformin and thiamine at transporters beyond OCT1 are needed to understand the role of metformin in thiamine disposition in other tissues. Finally, studies are clearly needed that differentiate the role of OCT1 in the cellular uptake of metformin and as a target for the drug.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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