EDITORIAL FOCUS | Pancreatic Physiology/Pathophysiology

Impact of prevailing thiamin levels on thiamin pyrophosphate uptake in pancreatic acinar cells: do the shuttle!

Lindsey Kennedy,1,3 Heather Francis,1,3 and Gianfranco Alpini1,2,3
1Research, Central Texas Veterans Healthcare System, Temple, Texas; 2Digestive Disease Research Center, Baylor Scott & White Health, Temple, Texas; and 3Medicine and Medical Physiology, Texas A&M Health Science Center, Temple, Texas

Submitted 17 August 2017; accepted in final form 21 August 2017

Thiamin is a water-soluble B1 vitamin that regulates critical cellular processes, such as oxidative energy metabolism, adenosine triphosphate (ATP) production, and mitochondrial function; thus, it is referred to as the energy vitamin (3, 5). Based on these known roles of thiamin, deficiency of this vitamin can lead to serious cellular impairments, including reduced cellular energy, increased oxidative stress, and mitochondrial dysfunction (2).

Pancreatic acinar cells (PACs) maintain a high degree of metabolic activity and therefore require larger amounts of thiamin (9); however, PACs are unable to synthesize their own thiamin and thus require thiamin via dietary or supplemental intake (16). Thiamin is taken up by the cell through thiamin transporter-1 and -2, is largely converted (80–90% of thiamin) into thiamin pyrophosphate (TPP), and is then transported into the mitochondria by the mitochondrial TPP transporter (MTPPT) (1). The MTPPT, encoded by the SLC25A19 gene, is a member of the mitochondrial carrier family (MCF), and previous work has shown that SLC25A19 promoter activity is driven by nuclear factor (NF)-Y function (7). Additionally, it has been shown that chronic exposure to alcohol and cigarette smoke affects mitochondrial TPP uptake in PACs (14, 15); however, it is unknown if extracellular thiamin levels affect this process as well. The function of the MTPPT shuttle is of clinical relevance since mutations in the transporter are linked to Amish congenital lethal microcephaly, as well as neuropathy and bilateral striatal necrosis (12, 13). Based on this information, this study by Sabu et al. (11), published in this issue of the American Journal of Physiology-Lung Cellular and Molecular Physiology, aimed to determine the effect of the prevailing level of thiamin on mitochondrial TPP uptake by PACs, using both PAC 266-6 (cultured PAC) and transgenic mice carrying the human SLC25A19 promoter.

In this study, the effects of thiamin levels on mitochondrial [3H]-TPP uptake were first shown in PACs maintained in either thiamin-deficient (thiamin-DEF) or oversupplemented (thiamin-OS) conditions (11). These initial results indicate that mitochondrial [3H]-TPP uptake was increased in PAC 266-6 maintained in thiamin-DEF conditions compared with thiamin-OS conditions. To corroborate these findings in an in vivo model, the authors fed mice either a thiamin-DEF or thiamin-OS diet and evaluated mitochondrial TPP uptake in hepatocytes. The authors argue that the use of hepatocytes for these studies is valid since it is difficult to obtain a sufficient concentration of PAC mitochondria for studies, 2) PACs and hepatocytes share the same embryonic lineage, and 3) this method has been used by other researchers (4, 6). Similar to the in vitro study, the authors found that mitochondrial [3H]-TPP uptake was increased in hepatocytes isolated from mice fed a thiamin-DEF diet versus mice fed a thiamin-OS diet. These findings are the first to indicate that prevailing thiamin levels regulate TPP shuttling in PACs. While the use of hepatocytes for these studies is experimentally valid, it may be beneficial in the future to look at isolated PACs; however, this may be dependent on the development of a method that isolates a larger concentration of PACs.

As previously stated, thiamin regulates ATP production; therefore, the authors evaluated the effect of extracellular thiamin levels on PAC 266-6 ATP production. Using the same in vitro studies as described above, the authors found that PAC 266-6 maintained in thiamin-DEF conditions had a significant reduction in ATP levels when compared with cells maintained in thiamin-OS conditions. In consideration that TPP taken up by the mitochondria acts as a cofactor for pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and branched-chain α-keto acid dehydrogenase, it is not surprising that thiamin deficiency leads to a decrease in ATP production (8, 13).

Since mitochondrial TPP uptake is regulated by the MTPPT, the authors examined the expression of MTPPT in PAC 266-6 maintained in either thiamin-DEF or thiamin-OS conditions. The results showed that PAC 266-6 cultured in thiamin-DEF conditions have a significant increase in both mRNA and protein levels of MTPPT when compared with thiamin-OS conditions. These findings were corroborated in vivo where the authors noted an increase in both mRNA and protein levels of MTPPT in hepatocytes isolated from mice fed a thiamin-DEF diet versus mice fed a thiamin-OS diet. These findings indicate that the increase in TPP uptake, in response to a thiamin-DEF surrounding, may be dependent on changes in expression of the MTPPT.

Based on the fact that the levels of MTPPT mRNA expression increase in response to increased thiamin levels, the authors suggest that this may be mediated by transcriptional changes in SLC25A19. Similar mechanisms have been shown to mediate the adaptive regulation of a multitude of other water-soluble vitamins (10). To evaluate this hypothesis, the authors evaluated the activity of the human SLC25A19 promoter (transfected into PAC 266-6) in both thiamin-DEF and thiamin-OS conditions. The authors found that SLC25A19...
activity was increased in PAC 266-6 cultured in thiamin-DEF conditions versus thiamin-OS conditions. To relate these findings to an in vivo model, the authors used their transgenic mice carrying the human SLC25A19 promoter (fused with firefly luciferase reporter gene), which has previously been characterized by this group (14), fed either a thiamin-DEF or thiamin-OS diet. Results from this study demonstrated that SLC25A19 activity is increased in hepatocytes isolated from transgenic mice fed a thiamin-DEF diet versus a thiamin-OS diet. These results suggest that PAC mitochondrial TPP uptake is dependent on adaptive-mediated transcriptional changes in SLC25A19, thereby affecting MTPPT expression. Additionally, the use of a transgenic mouse model expressing the human SLC25A19 gene is novel and brings about additional human relevance to the study.

Transcriptional changes in the SLC25A19 gene may be mediated by either nuclear factors that regulate basal activity of the promoter and/or epigenetic changes, such as histone modifications. To evaluate whether nuclear factors were regulating SLC25A19 promoter activity, PAC 266-6 were maintained in either thiamin-DEF or thiamin-OS conditions and the expression of NF-Y (a transcription factor known to regulate MTPPT expression) was evaluated. Results from this study found that there was no change in NF-Y mRNA levels in PAC 266-6 cultured in either condition. The authors then hypothesized that NF-Y may exhibit changes in binding affinity to the SLC25A19 promoter dependent on culture conditions. The authors found that NF-Y binding to the SLC25A19 promoter was significantly increased in PAC 266-6 cultured in thiamin-DEF conditions compared with thiamin-OS.

As previously discussed, epigenetic changes, such as histone modifications, may play an important role in the regulation of the expression of the SLC25A19 gene (14). Through in vitro analysis, the authors found that there was a significant increase in the euchromatin (activating) markers H3K4me3 and H3K9Ac in PAC 266-6 cultured in thiamin-DEF conditions versus thiamin-OS conditions; however, expression of the heterochromatin (repressing) marker H3K27me3 was significantly decreased in PAC 266-6 cultured in thiamin-DEF conditions versus thiamin-OS conditions. Overall, these findings allude to the role that thiamin levels may have on histone modification of the SLC25A19 gene, thereby regulating MTPPT uptake in PACs.

Little is known about how the TPP shuttling process is regulated in PACs; therefore, the findings of this study are noteworthy. This study is the first to identify that extracellular thiamin levels regulate mitochondrial TPP uptake and further expand the knowledge of the field. Additionally, the authors recognize that changes in uptake are dependent on transcriptional and epigenetic changes occurring in the SLC25A19 gene (encodes MTPPT). While it is interesting to note that both transcriptional and epigenetic changes are regulating MTPPT availability, these findings were from in vitro experimentation; therefore, additional work in in vivo models is necessary. Furthermore, these findings were in the context of normal PACs exposed to either thiamin-DEF or thiamin-OS conditions. It is important to understand if the changes noted are also occurring during diseased states. Since the authors have previously published data indicating that chronic exposure of PACs to alcohol negatively impacts MTPPT function through transcriptional and epigenetic changes (14), there may be a novel field for the development of therapeutics but further work is necessary. Furthermore, while the authors analyzed the molecular changes mediating mitochondrial TPP shuttling, they did not evaluate whether the changes in TPP uptake influenced the activity and/or viability of the cell. Since TPP is known to regulate oxidative stress and ATP production, which was reduced during thiamin-DEF conditions, it is intuitive that changes in these processes may impede cellular function.

Based on their findings, the authors come to the overall conclusion that PAC mitochondrial TPP uptake is adaptively regulated by extracellular thiamin levels, and this mechanism is partially regulated by both transcriptional and epigenetic changes in the SLC25A19 promoter. While their article is highly novel and presents interesting findings, there are more questions that need answering. In the future, it is imperative that additional work be performed to help completely elucidate the role of thiamin deficiency on MTPPT activity.

GRANTS

This effort for this editorial was supported in part by the Dr. Nicholas C. Hightower Centennial Chair of Gastroenterology from Baylor Scott & White and by a Veterans Affairs Research Career Scientist Award.

DISCLAIMERS

The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

L.K. and H.F. drafted manuscript; L.K., H.F., and G.A. approved final version of manuscript; H.F. and G.A. edited and revised manuscript.

REFERENCES


