Unraveling the pathophysiology of alcohol-induced thiamin deficiency

Paweł R. Kiela

Departments of Pediatrics and Immunobiology, University of Arizona Health Sciences Center, Tucson, Arizona

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IT TOOK OVER 4,500 YEARS FROM the first written description of beriberi in the Chinese medical book Neiching in 2687 B.C. until the first description of the causative “vitamin” deficiency by Polish scientist Casimir Funk in 1911 (1), and the biochemical description of thiamin pyrophosphate structure and its synthesis by Robert Williams in 1936 (11). Humans cannot synthesize thiamin, and it must therefore be obtained through dietary absorption in the intestine and reclaimed in the kidneys. Healthy adults require 1.4 mg of thiamin daily, a requirement further increased in children, during pregnancy, in critically ill patients, and in alcoholic subjects. While dietary deficiency remains the main contributing factor in Asia, chronic alcoholism is the primary cause of thiamin deficiency in Western countries and one of the leading causes of cognitive deficits, Wernicke’s encephalopathy, and Korsakoff psychosis (Wernicke-Korsakoff syndrome; WKS) associated with alcohol abuse. While chronic alcohol misuse does not result in encephalopathy if the dietary intake of thiamin is adequate, self-neglect, reduced intake of vitamins and minerals, low capacity of the liver to store thiamin, impaired conversion of thiamin to thiamin pyrophosphate, as well as decreased transport of thiamin across intestinal and/or renal epithelia are all believed to contribute to the development of cognitive and neurological deficits (8).

The cellular transport of thiamin is mediated by two specific carriers, thiamin transporter-1 (THTR1) and thiamin transporter-2 (THTR2), the products of the SLC19A2 and SLC19A3 genes, respectively. Interestingly, genetic studies with a group of alcoholic subjects affected by WKS and in supernormal controls identified several genetic variants in the SLC19A2 gene (2, 3), with two of the changes in the 3′-untranslated region of SLC19A2 region, potentially affecting gene expression. Deletion of the Slc19a2 gene (THTR1) in mice kept on a low-thiamin diet leads to diabetes, megaloblastic anemia, and sensorineural deafness (5, 6). The lack of significant changes in intestinal thiamin absorption reported by Reiding et al. (7) was attributed to a compensatory increase in THTR2 expression. On the other hand, deletion of Slc19a3 (THTR2) was reported by the same group to result in impaired intestinal thiamin absorption and decreased serum thiamin levels despite elevated THTR1 expression (7). Although THTR2-deficient mice displayed histological symptoms of hepatitis and renal interstitial inflammation and nephrosclerosis, they did not show overt histological changes in the brain (7). This could be explained by species specificity, or by a concerted functional interaction of the two thiamin transporters in maintaining adequate epithelial thiamin transport and cellular utilization of the vitamin. While mice deficient in both transporters (double knockout) have not yet been described, it is conceivable that a pathological processes in which both transporters are negatively affected would translate into more exacerbated phenotype.

In an issue of the American Journal of Physiology-Renal Physiology, Subramanian et al. (9) provide a novel and informative report that chronic alcohol consumption in rats fed a Lieber-DeCarli diet results in decreased carrier-mediated thiamin transport across the renal brush-border and basolateral membranes and in transcriptionally-mediated inhibition of the THTR1 and THTR2 expression. Moreover, the expression of thiamin pyrophosphokinase (TPKase), the rate-limiting enzyme in the synthesis of the coenzyme form of thiamin was modestly, albeit significantly reduced. This observation is consistent with the previously reported 27% decrease in the enzymatic activity of TPKase in the kidneys and other organs of rats chronically fed ethanol (4). The authors did not observe changes in the expression of the mitochondrial thiamin pyrophosphate carrier Slc25a19. In an article published in parallel in the American Journal of Physiology-Gastrointestinal and Liver Physiology, the same group provides additional evidence for detrimental effects of chronic alcohol administration on intestinal thiamin absorption, also accompanied by decreased transcription and expression of the Slc19a2 and Slc19a3 genes (10). While the transcriptional mechanisms at the level of Slc19a2 and Slc19a3 gene promoters remains to be determined, these two reports provide a significant advance in our understanding of alcohol-induced thiamin deficiency. In this case, the “two-hit” model is related not only to a simultaneous reduction of expression and activity of the two key thiamin carriers but also to the two affected sites of thiamin absorption. In alcoholic subjects, changes in thiamin supply combined with impaired epithelial thiamin transport and increased metabolic demand are likely the major factors contributing to alcohol-related brain damage.

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DISCLOSURES

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REFERENCES


