Comment on "Thiamine Deficiency Promotes T Cell Infiltration in Experimental Autoimmune Encephalomyelitis: The Involvement of CCL2"

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Zhe Ji et al. (1) reported that experimental autoimmune encephalomyelitis (induced either by MOG peptide immunization or by MOG-immune T cell transfer) was more severe in mice with thiamine deficiency (TD) than in mice without TD, and concluded that TD influences neuro-inflammation by upregulating the chemokine CCL2 and its receptor CCR2. We note that astrocytes (five times more abundant than neurons and major orchestrators of neuroinflammation) are particularly susceptible to TD. Astrocytes regulate water, ion and glutamate homeostasis and guard the blood–brain barrier. Acti-
vated as professional APCs, astrocytes produce numerous cyto-
kines, chemokines, and most complement proteins, and form a scar preventing inflammation spread (2). TD alters astrocytic expression of glutamate transporters (EAAT1 and EAAT2) and upregulates inflammatory genes and transcription factors controlling inflammatory genes (3). Three major astrocytic proteins are reduced in experimental TD: glial fibrillary acidic protein, glutamine synthetase, and a GABA transporter (GAT-3) (4, 5). Wernicke encephalopathy (WE) is the classic neurologic syndrome induced by TD. Neurymelities optica (NMO), an IgG-mediated astrocytopathy that targets aquaporin-4 water chan-
nels, is historically misdiagnosed as multiple sclerosis (6). Brain lesions occurring in NMO often localize in the aquaporin-4-enriched midline, as do lesions of WE (7). The implication of astrocytes as key players in NMO and WE pathophysiology supports the proposition that TD modulates neuroinflammation at the astrocyte level. Although impaired oxidative metabolism is a major initiator of WE, the interaction of TD and immune-mediated neurologic disorders is not generally appreciated. Thiamine merits consideration as an inexpensive supplementary therapeutic strategy for immune-mediated neurologic disorders.

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Abbreviations used in this article: NMO, neuromyelitis optica; TD, thiamine deficiency; WE, Wernicke encephalopathy.

References

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It is known that astrocytes are susceptible to thiamine deficiency (TD) and involved in TD-induced CNS damage/neuroinflammation. However, TD-induced neuroinflammation not only involves astrocytes, but also neurons, microglia, and endothelia cells. As previously demonstrated, TD produces a mild, chronic impairment of oxidative metabolism and reduced activities of the thiamine-dependent mitochondrial enzymes (1). TD causes regionally selective neuronal death as well as activation of astrocytes, microglia, and endothelial cells, which are also observed in various neurodegenerative disorders (1). TD induces a time-dependent chronic impairment of oxidative metabolism that initiates a cascade leading to selective neuronal loss that occurs first in the submedial thalamic nucleus in mice (2) and the mammillary bodies, the periaqueductal area, the periventricular region of the third ventricle, and the paramedian thalamic nuclei in humans (3). TD impacts neurons, microglia, and vascular structures at the early stage (4), while activating astrocytes at a later stage (5). TD induces expression of CD40 by the microglia and CD40L by astrocytes, and CD40–CD40L interaction may promote neuronal death (6). Deletion of CD40L delays the onset of TD-induced neuronal death as well as the activation of microglia and endothelial cells (7). Therefore, astrocytes are indeed involved in TD-induced neuroinflammation and CNS damage.

TD impairs glucose metabolism by inhibiting the activities of thiamine-dependent enzymes, including transketolase (TK), pyruvate dehydrogenase complex (PDHC), and α-ketogluta-
rate dehydrogenase complex (KGDHC) (1). TK is critical for production of NADPH, which is involved in free radical
metabolism. PDHC and KGDHC are two important protein complexes in the mitochondria, and play a critical role in mitochondria functions in tricarboxylic acid cycle (8). The inhibition of these three enzymes causes mitochondrial dysfunction, energy shortage, and chronic oxidative stress. Previous studies reveal that the mild oxidative stress induces a series of inflammatory processes including microglia activation in vulnerable regions of TD mice (4, 9). Recent studies show that neuronal induction of monocyte chemoattractant protein-1 during TD causes microglia recruitment and activation, which exacerbates neurodegeneration (10).

In the elderly, inadequate thiamine intake and TD is common (11), which may induce mitochondrial dysfunction, chronic oxidative stress, neurodegeneration, and depression. According to the 2002 China Health and Nutrition Survey, 79% of Chinese had thiamine levels below the recommended nutrient intake. A recent study indicated a poor thiamine nutritional status in Chinese aged between 50–70 years (12). Thiamine supplementation is associated with mood improvements (13), cognitive improvement (14), and Alzheimer’ disease–related behavioral and pathological recovery (15). Therefore, thiamine supplementary therapeutic strategy is not only for immune-mediated neurologic disorders, but also for age-related neurodegenerative diseases, such as Alzheimer’s disease.

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Abbreviations used in this article: KGDHC, α-ketoglutarate dehydrogenase complex; PDHC, pyruvate dehydrogenase complex; TD, thiamine deficiency; TK, transketolase.

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