Role of Mitochondrial Dysfunction and Oxidative Stress in the Pathogenesis of Selective Neuronal Loss in Wernicke’s Encephalopathy

Paul Desjardins and Roger F. Butterworth*

Neuroscience Research Unit, CHUM (Hôpital St-Luc), University of Montreal, Montreal, Quebec, Canada

Abstract

Thiamine deficiency results in Wernicke’s encephalopathy and is commonly encountered in chronic alcoholism, gastrointestinal diseases, and HIV AIDS. The earliest metabolic consequence of thiamine deficiency is a selective loss in activity of the thiamine diphosphate-dependent enzyme α-ketoglutarate dehydrogenase (α-KGDH), a rate-limiting tricarboxylic acid cycle enzyme. Thiamine deficiency is characterized neuropathologically by selective neuronal cell death in the thalamus, pons, and cerebellum. The cause of this region-selective neuronal loss is unknown, but mechanisms involving cellular energy failure, focal lactic acidosis, and NMDA receptor-mediated excitotoxicity have classically been implicated. More recently, evidence supports a role for oxidative stress. Evidence includes increased endothelial nitric oxide synthase, nitrotyrosine deposition, microglial activation, and lipid peroxidation. Reactive oxygen species production results in decreased expression of astrocytic glutamate transporters and decreased activities of α-KGDH, resulting in an amplification of cell death mechanisms in thiamine deficiency.

Index Entries: Thiamine deficiency; Wernicke–Korsakoff; oxidative stress; mitochondrial dysfunction; neuronal cell death; reactive oxygen species; nitric oxide synthase; thalamic lesions.
from poor diet and impaired absorption of thiamine from the gastrointestinal tract. In addition, alcohol impairs the phosphorylation of thiamine both in peripheral tissues and in brain.

Neuropathologic evaluation of brain tissue from WKS patients reveals a pattern of selective symmetrical damage to mammillary bodies, thalamus, cerebellum, and pons (1). Cellular changes include neuronal loss, astrocytic proliferation, and microglial activation. The cause of this distinctive pattern of neuronal loss has not been fully elucidated. However, several theories involving cellular energy failure, focal lactic acidosis, blood–brain barrier breakdown, and NMDA-receptor-mediated excitotoxicity have been proposed. In experimental animals exposed to thiamine deficiency, both apoptotic and necrotic patterns of neuronal cell death have been observed.

In the 1930s, Peters and co-workers showed that thiamine deficiency in pigeons resulted in the accumulation of lactate in the brainstem of affected birds (2). Furthermore, they showed that the addition of small quantities of crystalline thiamine to the isolated brainstem tissue from thiamine-deficient birds in vitro resulted in normalization of lactate levels. These findings led to the formulation of the concept of “the biochemical lesion” in thiamine deficiency. Later studies showed that the enzyme defect responsible for the “biochemical lesion” was α-ketoglutarate dehydrogenase (α-KGDH) rather than pyruvate dehydrogenase (PDHC) (as had initially been suspected). α-KGDH and PDHC are major thiamine diphosphate (TDP)-dependent enzymes involved in brain glucose oxidation (Fig. 1).

In the brain, as in most mammalian cells, thiamine occurs predominantly (over 80%) in the form of TDP, the remainder being made up of thiamine monophosphate (10%) and thiamine triphosphate (5–10%), with only trace amounts of free thiamine. Thiamine is transported into the brain and phosphorylated by the action of thiamine pyrophosphokinase and inhibition of this enzyme by thiamine antagonists such as pyrithiamine results in a generalized reduction of TDP concentrations throughout the brain and an early selective loss in activity of α-KGDH in regions of the brain such as thalamus, which are destined to manifest selective neuronal cell loss (3). Decreased activities of α-KGDH following treatment with pyrithiamine are associated with decreased synthesis of glucose-derived excitatory and inhibitory amino acids, including glutamate, aspartate, and GABA, with a concomitant increase in lactate and alanine (4) consistent with decreased flux of carbon through the tricarboxylic acid cycle. Both the α-KGDH decreases and the changes in synthesis of amino acids are initially reversible following thiamine rehabilitation in pyrithiamine-treated animals (4), suggesting that these changes are an integral part of “the biochemical lesion” originally proposed by Peters.

In a study of thiamine-dependent enzymes in postmortem brain tissue from alcoholic patients, it was reported that decreased activities of PDHC, α-KGDH, and transketolase were confined to those cases in which the neuropathologic diagnosis of WKS had been made (5). Alcoholic patients dying in hepatic coma without WKS manifested brain TDP-dependent enzyme activities within normal limits. Furthermore, activities of a non-TDP-dependent enzyme glutamate dehydrogenase were unchanged in both WKS and non-WKS alcoholic brains. These findings provide evidence, for the first time, that reduction in thiamine-dependent enzymes are implicated in the pathogenesis of WKS in humans.

Mitochondrial Dysfunction, Lactic Acidosis, and Brain Energy Failure in Thiamine Deficiency

Oxidative decarboxylation of α-ketoglutarate (and pyruvate) are reportedly decreased in isolated mitochondria from the brains of pyrithiamine-treated rats (6), consistent with reductions in the activity of α-KGDH. Furthermore, normal rates of pyruvate decarboxyla-