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Review

The impact of oxidative stress in thiamine deficiency: A multifactorial targeting issue

Alan S. Hazell [a,b,*], Samantha Faim [b], Guilherme Wertheimer [b], Vinicius R. Silva [b], Cleiton S. Marques [b]

[a] Department of Medicine, University of Montreal, Montreal, Quebec, Canada
[b] Departamento de Neurologia, Universidade Estadual de Campinas (UNICAMP), Campinas, São Paulo, Brazil

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ABSTRACT

Thiamine (vitamin B1) deficiency, the underlying cause of Wernicke–Korsakoff syndrome, is associated with the development of focal neuronal loss in vulnerable areas of the brain. Although the actual mechanism(s) that lead to the selective histological lesions characteristic of this disorder remain unresolved, oxidative stress has been shown to play a major role in its pathophysiology. In this review, the multifactorial influence of oxidative stress on a variety of processes known to take part in the development of structural lesions in TD including excitotoxicity, neuroinflammation, blood–brain barrier integrity, mitochondrial integrity, apoptosis, nucleic acid function, and neural stem cells will be discussed, and therapeutic strategies undertaken for treating neurodegeneration examined which may have an impact on the future treatment of this important vitamin deficiency.

1. Introduction

Vitamin B1 (thiamine) deficiency is a disorder involving impairment of oxidative metabolism in which selective cerebral vulnerability is a major consequence. This is manifested in the form of Wernicke–Korsakoff syndrome (WKS), a serious and potentially life-threatening neuropsychiatric disorder (Carmichael and Stern, 1931) consisting of Wernicke's encephalopathy (WE), the neurological component of the disorder characterized by acute thiamine deficiency (TD) in association with confusion, ophthalmoplegia, and ataxia but no permanent structural damage, and Korsakoff's psychosis, a debilitating amnesic state due to chronic TD and accompanied by irreversible diencephalic lesions. Neuropathologically, the disorder is characterized by focal areas of the brain developing symmetrical hemorrhagic and ischemic-like lesions, occuring most frequently in diencephalic structures, in particular the thalamus and mammillary bodies (Fig. 1), extending caudally through the midbrain (inferior colliculus) and brainstem areas that include the vestibular nuclei and inferior olivary complex (Victor et al., 1989).

2. Pathophysiology of thiamine deficiency

The pathophysiological mechanisms involved in TD are complex. Four major enzyme systems utilize thiamine in the form of thiamine diphosphate (TDP) as a major cofactor, i.e. pyruvate dehydrogenase (EC 1.2.4.1) complex (PDHC), an organized enzyme assembly that connects glycolysis with the tricarboxylic acid (TCA) cycle, α-ketoglutarate dehydrogenase (EC 1.2.4.2) complex (KGDHC), a multicomponent enzyme complex associated with the TCA cycle, transketolase (EC 2.2.1.1) (TK), a key participant in the pentose phosphate shunt involved in nucleic acid and lipid biosynthesis, and branched-chain α-ketoacid dehydrogenase (EC 1.2.4.4) complex (BCKDHC) involved in accumulation of the branched chain amino acids leucine, isoleucine, and valine (Wendel et al., 1983), and which is associated with a rare inborn error of metabolism, maple syrup urine disease. Chronic thiamine deprivation is accompanied by region-selective reductions in levels of thiamine-dependent enzymes in brain (Butterworth, 1986), including KGDHC and TK (Fig. 2). While the exact role of PDHC, BCKDHC and transketolase remains unclear in the development of thiamine-deficiency induced lesions, KGDHC appears to be responsible for many of the reversible changes accompanying TD (Gibson et al., 1984; Butterworth and Heroux, 1989) (see Fig. 2). During experimental TD, onset of neurological symptoms occurs when TDP concentrations fall to less than 15% of normal values, and these reductions in TDP levels are accompanied by reductions

Abbreviations: AD, Alzheimer's disease; ATP, adenosine triphosphate; BBB, blood–brain barrier; eNOS, endothelial nitric oxide synthase; GFAP, glial fibrillary acidic protein; GLT-1, glutamate transporter 1; GLAST, glutamate/aspartate transporter; KGDHC, α-ketoglutarate dehydrogenase complex; MAO, monoamine oxidase; NMDA, *N*-methyl-D-aspartate; PD, Parkinson's disease; ROS, reactive oxygen species; SINDEPAR, Sinemet-Deprenyl-Parlodel; TCA, tricarboxylic acid cycle; TD, thiamine deficiency; TSPO, translocator protein (18 kDa); WKS, Wernicke–Korsakoff syndrome.

* Corresponding author. Address: NeuroRescue Laboratory, Hôpital Saint-Luc (CHUM), 1058 St-Denis, Montreal, Quebec, Canada H2X 3J4. Tel.: +1 (514) 890 8310x35740/58; fax: +1 (514) 412 7737.
E-mail address: alan.stewart.hazell@umontreal.ca (A.S. Hazell).

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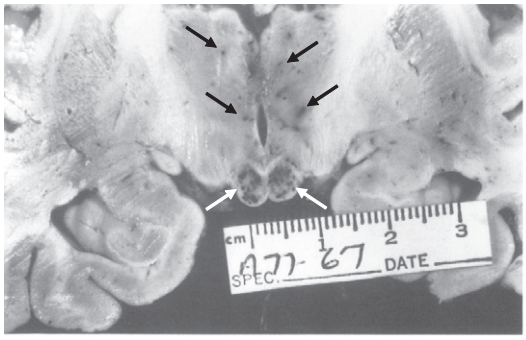

Fig. 1. Pathological hallmarks of Wernicke's encephalopathy. The brain is sectioned coronally at the level of the thalamus with black arrows showing structural lesions (dark areas) in this brain region. Lowest pair of arrows indicate the mammillary bodies, also showing considerable histological damage. *Modified from Victor et al. 1989, with permission.*

in KGDHC activity in both affected animals (Héroux and Butterworth, 1995) and in autopsied brain tissue from alcoholic patients with neuropathologically-confirmed WKS (Butterworth et al., 1993).

During TD, decreased ATP production, pyruvate accumulation and lactate production are a consequence of inhibition of oxidative decarboxylation of pyruvate and α-ketoglutarate (Aikawa et al., 1984; Navarro et al., 2005) (Fig. 2). Unless thiamine is rapidly supplemented, acidosis and death can occur within twenty four hours. Areas of increased lactic acidosis in brain are localized to regions that subsequently develop histological lesions (McCandless, 1982; Hakim, 1984; Munujos et al., 1993), and probably play a significant role in the pathophysiology.

3. Oxidative stress and excitotoxicity in TD

Considerable evidence for development of oxidative stress has been demonstrated in TD, including the presence of increased production of reactive oxygen species (ROS) (Langlais and Zhang, 1997), and increased expression of heme oxygenase (HO-1) and intercellular adhesion molecule-1 (ICAM-1) (Gibson and Zhang, 2002) as well as microglial activation (Todd and Butterworth, 1999), along with induction of the endothelial isoform of nitric oxide synthase (eNOS) (Hazell and Butterworth, 2009). Moreover, selective induction of the endothelial isoform of nitric oxide synthase (eNOS) has been reported in the brains of TD animals. Significant complications of oxidative stress include changes in the levels of superoxide dismutase and apoptosis (Kokoszka et al., 2001) which are also reported to occur in TD (Calingasan and Gibson, 2000; Matsushima et al., 1997).

Considerable evidence have been provided for the existence of excitotoxic-mediated cell death in TD. Reduced incorporation of [^{14}C]-glucose into glutamate (Gaitonde et al., 1975) is consistent with reduced activities of KGDHC, resulting in reduced energy status in TD animals (Aikawa et al., 1984). In addition, decreased neuronal damage was reported following treatment with the noncompetitive NMDA glutamate receptor antagonist MK-801 (Langlais and Mair, 1990). We and others first reported focal increases in extracellular glutamate concentration that was restricted to vulnerable brain regions in TD (Hazell et al., 1993;

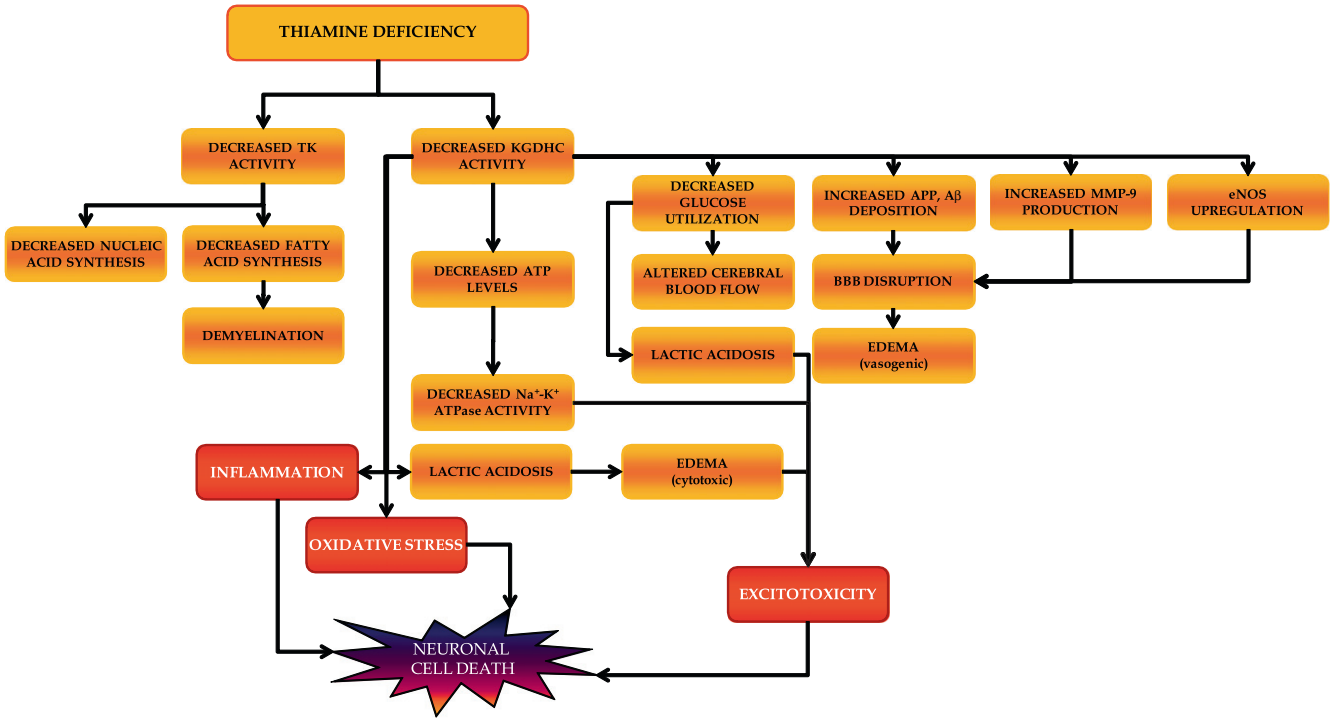

Fig. 2. Diagram showing a number of key components of the event cascade associated with focal vulnerability in thiamine deficiency (TD). Biochemical changes due to TD include decreased activity of the thiamine-dependent enzymes α-ketoglutarate dehydrogenase complex (KGDHC) and transketolase (TK). Reduced activity of KGDHC leads to wide-ranging effects that include development of energy deficits due to resulting impairment of the TCA cycle producing diminished Na^+–K^+–ATPase activity and excitotoxic conditions which can ultimately lead to cell death. Decreased KGDHC function also results in the development of lactic acidosis in response to impaired TCA cycle activity. This acidosis can contribute to cytotoxic brain edema, a contributor to excitotoxicity. Impaired mitochondrial function involving diminished KGDHC activity also leads to a net increase in ROS production and oxidative stress along with development of inflammatory processes, both of which can result in cell death. Compromised mitochondrial function associated with decreased KGDHC activity also leads to increased net ROS production that contributes to neuronal dysfunction and cell death. Impaired KGDHC activity due to TD results in decreased glucose utilization that leads to alterations in cerebral blood flow, along with compensatory stimulation of lactic acidosis. KGDHC impairment also results in increase in production of amyloid precursor protein (APP) and amyloid-β (Aβ) peptide formation, increased synthesis of matrix metalloproteinase-9 (MMP-9), and upregulation of endothelial nitric oxide synthase (eNOS), all of which contribute to blood–brain barrier breakdown (BBB). BBB disruption then leads to vasogenic edema. Reduced TK activity results in decreased fatty acid synthesis that can lead to demyelination, and decreased nucleic acid synthesis.