Neurochemistry International 55 (2009) 129–135

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/neuint

Astrocytes are a major target in thiamine deficiency and Wernicke's encephalopathy

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ARTICLE INFO

Article history:
Received 2 December 2008
Received in revised form 25 February 2009
Accepted 27 February 2009
Available online 9 March 2009

Keywords:
Thiamine deficiency
Glutamate
Excitotoxicity
Astrocyte
EAAT
Inflammation
Vitamin B_1
Oxidative stress

ABSTRACT

Thiamine deficiency (TD) is the underlying cause, and an established model, of Wernicke's encephalopathy (WE). Although the neurologic dysfunction and brain damage that results from TD has been well-described, the precise mechanisms that lead to the selective histological lesions characteristic of this disorder remain a mystery. Over the course of many years, various processes have been proposed that could lead to focal neuronal cell death in this disorder. But despite a concerted effort to relate these processes to a clear sequelae of events culminating in development of the focal neuropathology, little success has resulted. In recent years, however, a role for astrocytes in the pathophysiology of TD has been emerging. Here, alterations in glutamate uptake, and levels of the astrocytic glutamate transporters EAAT1 and EAAT2 in TD and WE, are discussed in terms of an excitotoxic event, along with the GABA transporter subtype GAT-3, and changes in other astrocytic proteins including GFAP and glutamine synthetase. Lactic acidosis, changes in the water channel protein AQP-4 and brain edema are also a focus of attention in relation to astrocyte dysfunction, while involvment of oxidative stress and inflammatory processes, along with white matter injury in terms of excitotoxicity are other key issues considered. In summary, a new appraisal of the extent of involvement of astrocytes in TD and WE is presented, with the evidence suggesting these cells represent a major target for damage during the disease process.

1. Introduction

Cerebral damage is a major consequence of thiamine deficiency (TD), the underlying basis of Wernicke's encephalopathy (WE), one of the two components of the neuropsychiatric disease complex, the Wernicke–Korsakoff syndrome. In the developed world, WE occurs principally in cases of chronic alcoholism, although it can also develop in other non-alcoholic conditions (Shah and Wolff, 1973; Ebels, 1978; Lindboe and Loberg, 1989; Butterworth et al., 1991). Selective cerebral vulnerability is a major consequence of WE, in which focal areas of the brain exhibit symmetrical areas of profound neuronal loss and accompanying gliosis, occurring most frequently in diencephalic regions such as the thalamus and mammillary bodies (Victor et al., 1989). Lesions also extend caudally through midbrain structures such as the inferior colliculus and other periventricular brainstem areas that include the vestibular nuclei and inferior olivary complex in particular.

WE is surprisingly difficult to diagnose during life, with the classical triad of clinical features of ophthalmoplegia, gait ataxia and a confusional state often being absent in both alcoholic and non-alcoholic cases, leading to only a 20% success rate (Harper, 1983). Evidence from studies in a large Australian population suggests that the incidence of WE is higher than anticipated (1.7%), with 88% of these cases being alcohol-related (Harper, 1979). This finding suggests a higher incidence than of other disorders such as epilepsy and Parkinson's disease, making WE an important health care issue. Although acute bouts of WE are readily treatable nowadays by administration of thiamine in the emergency room, neuropathology due to chronic WE can develop following repeated bouts of "subclinical" TD (Harper, 1983), suggesting that appropriate intervention during these episodes has the potential to delay or prevent the development of major histological lesions. Such intervention, however, is only possible, and likely to succeed, if the underlying pathophysiology of this condition is well understood, something that remains seriously lacking at the present time. Over the years, a number of potential mechanisms have been suggested to play a major role in the underlying pathology. These include alterations in acetylcholine synthesis (Gibson et al., 1984) and gamma-aminobutyric acid (GABA) levels (Héroux and Butterworth, 1988), changes in cerebral glucose utilization (Hakim and Pappius, 1983), oxidative stress (Langlais et al., 1997; Calingasan

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0197-0186/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuint.2009.02.020

and Gibson, 2000; Hazell and Wang, 2005), lactic acidosis and decreased brain pH (Hakim, 1984; Navarro et al., 2005), apoptosis (Matsushima et al., 1997), alterations in cerebral blood flow (Hakim, 1986), inflammatory processes (Todd and Butterworth, 1999; Ke et al., 2006; Vemuganti et al., 2006), and excitotoxicity (Hazell et al., 1993). Recently, emphasis is being placed on astrocytes and their involvement in cerebral injury and neurodegenerative disease (Maragakis and Rothstein, 2006). In addition, evidence suggests that astrocytes may be targeted in TD, and possibly WE. This paper will focus on current trends in our understanding of the role of astrocytes in TD pathophysiology, and how these cells may represent a major target of the disease process.

2. Astrocytes and glutamate-mediated excitotoxicity in TD and WE

Astrocytes play a crucial role in brain including regulation of K^+ levels (Gardner-Medwin et al., 1981; D'Ambrosio et al., 2002), inactivation of released neurotransmitters (Schousboe, 1981), trafficking of metabolites (Hertz et al., 1999), and brain water homeostasis (Walz, 1987). Amongst the plethora of functions is the rapid and efficient removal of glutamate from the extracellular space (Drejer et al., 1983), a process that is instrumental in maintaining normal interstitial levels of this neurotransmitter (Nicholls and Attwell, 1990).

Over the years, a number of studies have identified glutamate as being involved in the pathophysiology of TD. Armstrong-James et al. (1988) reported a similarity in the appearance and development of the central thalamic lesion in TD to that observed following intrathalamic administration of excitatory amino acids. Earlier reports of glutamate levels being reduced in whole brain of TD animals (Gubler et al., 1974) were consistent with decreases in the conversion of [^{14}C]glucose to glutamate in TD rats (Gaitonde et al., 1975) and reduced Ca^{2+}-dependent release of glutamate in hippocampal slices from symptomatic TD animals (Lê et al., 1991), suggesting a role for glutamate in this disorder. Treatment with the noncompetitive NMDA receptor antagonist MK-801 was also shown to lead to a reduction in the extent of neuronal damage in TD rats (Langlais and Mair, 1990). In 1993, the first direct evidence that histological vulnerability in the thalamus of TD rats was associated with focal increases in extracellular glutamate concentration was demonstrated (Hazell et al., 1993; Langlais and Zhang, 1993). This was later found to be associated with a dramatic loss of the glutamate transporters EAAT1 and EAAT2 (Hazell et al., 2001) (Fig. 1). These two transporters are predominantly localized in astrocytes (Danbolt et al., 1992; Rothstein et al., 1994; Lehre et al., 1995), and are responsible for the major spatial buffering capacity of extracellular glutamate in brain (Danbolt, 2001). Downregulation of these two glutamate transporters can have serious consequences in terms of the astrocyte to maintain normal levels of interstitial glutamate, and can therefore lead to sustained depolarization of the tissue, excitotoxic damage, and ultimately neuronal cell death (Rothstein et al., 1996). Further evidence of astrocyte compromise was reported in a recent study (Hazell et al., in press), in which the central portion of the thalamus of TD rats showed a profound loss of glial fibrillary acidic protein (GFAP) and glutamine synthetase, two proteins found predominantly in astrocytes, along with a large decrease in GAT-3, a GABA transporter which, in the thalamus, is localized predominantly in these glial cells (De Biasi et al., 1998) (Fig. 1). These findings suggest that TD either produces a massive downregulation of astrocyte-specific proteins, or that TD results in the death of thalamic astrocytes. In any event, the results provide strong evidence that astrocytes are being targeted in TD in this vulnerable brain region. Furthermore, in the same study, it was

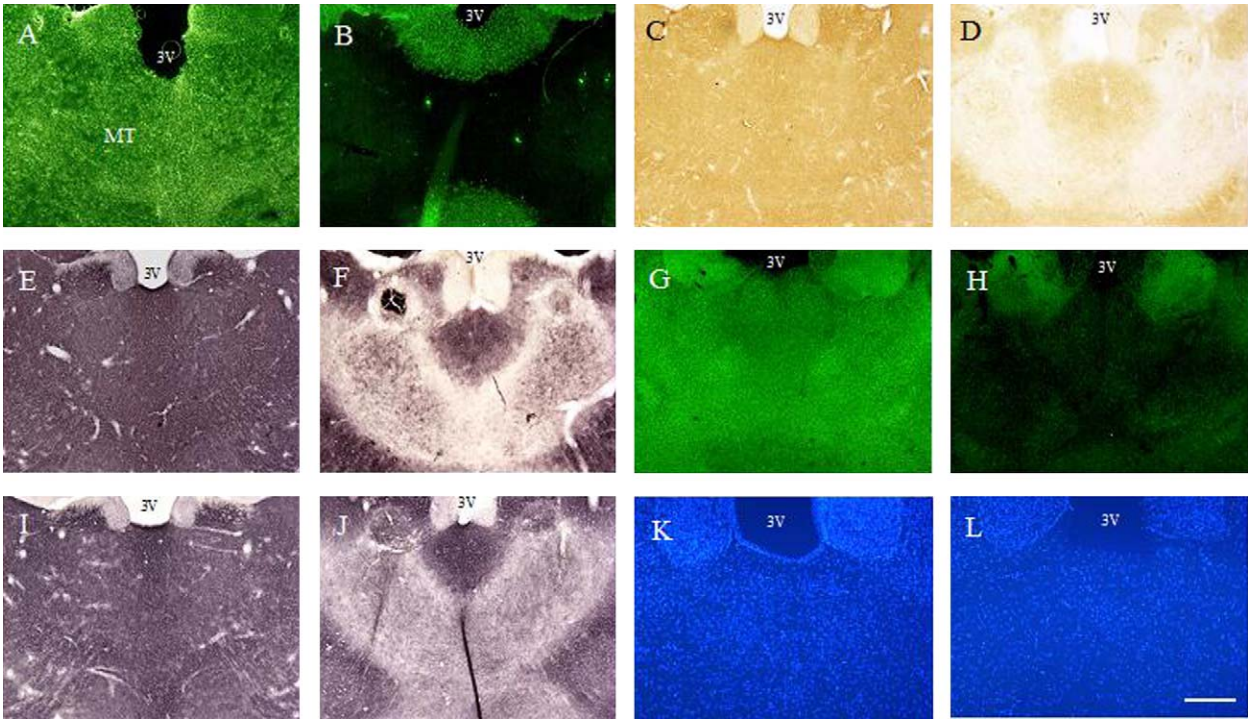

Fig. 1. Photomicrographs of representative sections of brain from TD rats at the level of the posterior thalamus. Immunohistochemical staining indicates massive loss of GFAP (A and B), EAAT1 (C and D), EAAT2 (E and F), GS (G and H), and GAT-3 (I and J) immunoreactivities in the area of the medial thalamus in TD (B, D, F, H, and J) compared with pair-fed control animals (A, C, E, G, and I), suggesting either profound downregulation of these astrocyte-specific markers or a considerable loss of astrocytes. Staining with DAPI (K and L) indicates the presence of decreased cell nuclei but no pannecrosis in the medial thalamic region. MT, medial thalamus; 3V, third ventricle. Bars: A–J, 600 μm; K and L, 200 μm. Adapted from Hazell et al. (in press), with permission.