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Review

Brain and behavioral pathology in an animal model of Wernicke's encephalopathy and Wernicke–Korsakoff Syndrome

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ABSTRACT

Animal models provide the opportunity for in-depth and experimental investigation into the anatomical and physiological underpinnings of human neurological disorders. Rodent models of thiamine deficiency have yielded significant insight into the structural, neurochemical and cognitive deficits associated with thiamine deficiency as well as proven useful toward greater understanding of memory function in the intact brain. In this review, we discuss the anatomical, neurochemical and behavioral changes that occur during the acute and chronic phases of thiamine deficiency and describe how rodent models of Wernicke–Korsakoff Syndrome aid in developing a more detailed picture of brain structures involved in learning and memory.

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Abbreviations: 5-HT, serotonin; αKGDH, alpha-ketoglutarate dehydrogenase; ACh, acetylcholine; AChE, acetylcholinesterase; AVVL, anteroventral ventrolateral; DA, dopamine; DB, diagonal band; GABA, gamma-aminobutyric acid; ILn, intralaminar nucleus; IML, internal medullary lamina; MRI, magnetic resonance imaging; MS, medial septum; MTP, matching-to-position; MWM, Morris water maze; NE, norepinephrine; NO, nitric oxide; NMTP, nonmatching-to-position; PFC, prefrontal cortex; PTD, pyrithiamine-induced thiamine deficiency; ROS, reactive oxygen species; TCA, tricarboxylic acid; TD, thiamine deficiency; TPP, thiamine pyrophosphate; WE, Wernicke's encephalopathy; WKS, Wernicke–Korsakoff Syndrome; VPL, ventroposterolateral

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1. Introduction

Studies in rodent models have provided greater understanding of the neurobiology of memory and memory dysfunction. In particular, rodent models have been developed and extensively validated for human memory disorders such as Alzheimer's disease, age-related memory loss, and temporal lobe damage-associated amnesia. For example, transgenic mice carrying mutation/deletion of Alzheimer's disease-associated genes are now revealing the anatomical and functional consequences of fibrillar amyloid deposits (Grutzendler et al., 2007; Yang et al., 2005). Likewise, studies with aged rats and mice are elucidating the anatomical and physiological changes that occur in hippocampal circuits which lead to age-related memory decline (Erickson and Barnes, 2003; Krause et al., 2008; Oler and Markus, 2000; Shen et al., 1997).

Despite extensive study on the role of the hippocampus and medial temporal lobe structures, identification of other brain areas critical for normal memory function is still debated. In the present review, we describe our work using a rodent model of Wernicke–Korsakoff Syndrome (WKS), a neurodegenerative disorder caused by thiamine (vitamin B1) deficiency, to study the role of various brain structures on memory and WKS dementia/learning deficits. This model recapitulates thiamine deficiency (TD) observed in WKS patients as well as the cognitive/memory deficits that are a cardinal feature of WKS. We discuss how the use of this model has revealed a number of neurochemical, neuroanatomical and behavioral changes that occur in various regions of the brain at the acute and chronic stages of TD.

2. Structural, neurochemical and behavioral pathology associated with rodent models of Wernicke's encephalopathy and Wernicke–Korsakoff Syndrome

TD induces severe CNS dysfunction leading to several disorders including: beriberi, Wernicke's encephalopathy, and the amnestic disorder WKS. First described in the late 19th century (Thomson et al., 2008), the cause of TD was almost exclusively due to dietary insufficiency, a finding that was instrumental to the early discovery of vitamins and their role in human health and nutrition. Despite the fact that TD due to dietary insufficiency has been largely eradicated in industrialized countries following the establishment of food fortification and vitamin supplementation programs, TD is still a problem in adults with chronic alcoholism due to poor diet and nutritional malabsorption. In addition, TD continues to be problematic in developing nations where adequate nutrition is lacking (Harper, 2006). Genetic mutation of genes such as *Slc19A2* or *Slc19A3* which code for thiamine transporters (Guerrini et al., 2005; Kono et al., 2009) or the transketolase-like 1 gene (*Tktl1*) which affects thiamine pyrophosphate binding, is thought to potentially predispose individuals (especially alcoholics) who have diets with low/lacking thiamine to WE and WKS (Coy et al., 1996, 2005). More recently, TD has been observed in an increasingly diverse clinical spectrum (reviewed in Sechi and Serra, 2007) including after gastrointestinal surgery and in individuals with AIDS, Crohn's disease, eating disorders, renal disease, cancer, etc. (Parkin et al., 1991, 1993; Saad et al., 2010). Thus, brain and behavioral changes following TD is a clinically-relevant area of study with broad implications for a wide range of affected individuals.

Neurological manifestations of TD were first described by Carl Wernicke in the late 19th century and included a triad of symptoms including ataxia (loss of coordinated muscle movement), nystagmus (involuntary eye movement) or ophthalmoplegia (eye movement paralysis) and "confusion" or change in consciousness/mental status (Thomson et al., 2008; reviewed in Sechi and Serra, 2007). For his discovery, this condition now bears Wernicke's name and is known as Wernicke's encephalopathy (WE). Soon after Wernicke's description, Sergei Korsakoff described a similar condition observed in chronic alcoholics that was characterized by severe memory deficits (Korsakoff, 1889), not knowing that these individuals suffered from WE. Thus, TD can result in WE which can culminate in death if left untreated (~20% of cases) or advance into WKS in ~85% of patients (Day et al., 2004; Harper et al., 1986).

A number of brain and behavioral changes accompany acute and chronic TD that can be investigated using rodent models (Table 1). Similar to that observed in humans, TD in rodents can be fatal and results in a neurological phenotype with striking similarity to that seen in humans (discussed below). In particular, histopathological studies in humans and rodents have demonstrated that prolonged TD produces similar time-dependent cell death, glial activation, inflammation, abnormalities in oxidative metabolism, and/or degeneration of neural tissue (Langlais, 1995; Zhang et al., 1995), suggesting a similar role played by thiamine in the human and rodent brain. In particular, our TD rodent model recapitulates the characteristic lesions seen in affected individuals with WE as well as the accompanying memory deficits that are characteristic of WKS. We review the brain and behavioral changes in rodent models that occur during (acute WE phase) and after recovery (chronic WKS phase) of TD and compare these results with findings in humans.

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