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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.

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 (Yang et al., 2005; Grutzendler et al., 2007). 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 are 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

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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.

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 amnesic 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, 1955), 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 (Harper et al., 1986; Day et al., 2004).

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.

Rodent Models of Wernicke Encephalopathy and Wernicke-Korsakoff Syndrome

There are two types of experimental rodent models of TD that have been studied in detail. The first approach induces TD via feeding of thiamine-free food to rodents for an extended period of time sufficient to deplete thiamine stores (3–4 weeks). The second approach generates TD more quickly by combining the feeding of a thiamine free diet in addition to administration (i.p. injection) of a thiamine pyrophosphokinase inhibitor, such as pyriethamine. This second model, termed pyriethamine-induced thiamine deficiency (PTD), induces a stereotyped progression of neurological/behavioral symptoms that have been mapped to specific pathological changes in anatomy and neurochemistry (Zhang et al., 1995; Hazell and Butterworth, 2009) and mimic the pathology described in humans with TD. Moreover, both human clinical reports (Cook and Thomson, 1997; Thomson and Cook, 1997, Cook, 2000; Thomson et al., 2002; Agabio, 2005; Kopelman et al., 2009;) and studies in rodent models of TD (Langlais, 1995) demonstrate that WE symptoms can be treated with high doses of thiamine (e.g. minimum of 500 mg thiamine three times daily, for at least 2 days in WE patients; Agabio, 2005) which may prevent the development WKS in both species. Thus, the validity of rodent models of TD center upon the replication of both acute neurological symptoms observed in the WE phase and the permanent cognitive changes that define the amnesic disorder of WKS. Therefore, the strength of these rodent models come from the ability to manipulate the timing and duration of TD, the timing and nature of therapeutic interventions, and the time at which anatomical and/or physiological indices are measured.

I. Cytopathological, Neurochemical and Behavioral Changes During the Acute WE Stage of Thiamine Deficiency

Cytopathology—Thiamine plays a key role in the maintenance of normal cellular function and because of its high oxidative metabolism, the CNS is particularly vulnerable to TD. Deficiencies of thiamine lead to disruption of several enzymatic pathways that are crucial for proper cellular and metabolic function (Butterworth, 1986a; Butterworth et al., 1986b, 1993a; Sheu et al., 1998). TD in humans and rodents reduces levels of thiamine pyrophosphate (TPP), a coenzyme necessary for the catalysis of enzymatic systems involved in cerebral glucose utilization (Heroux and Butterworth, 1995; Mancinelli et al., 2003). The reduction in TPP synthesis in turn disrupts the formation of TPP-associated enzymes. For example, decreased levels of the TPP-dependent enzyme alpha-ketoglutarate dehydrogenase (α KGDH) have been consistently observed in individuals with WKS as well as in the PTD model (Gibson et al., 1984; Butterworth et al., 1986a, b; Sheu et al., 1998). Serving as an important intermediate in the tricarboxylic acid (TCA) cycle, an enzymatic process essential for adenosine triphosphate synthesis, diminished α KGDH activity disrupts mitochondrial glucose oxidation resulting in cell death (Gibson et al., 1984). Consequently, oxidative stress as been implicated in the acute cytopathology induced by TD.

Recent studies further confirm the role of oxidative stress in the neuropathology associated with TD. Elevated levels of oxidative stress indicators such as hemeoxygenase-1 and intracellular cell adhesion molecule-1, have been reported in the brains of TD rats (Calingasan and Gibson, 2000b; Gibson and Zhang, 2002). TD-induced impairments in oxidative capacity also accelerate endothelial nitric oxide synthase expression leading to excessive nitric oxide (NO) production (Calingasan and Gibson, 2000a). This finding may be of particular significance as NO can interact with the free radical superoxide to form

peroxynitrite, a powerful oxidant associated with cell toxicity and damage (Hazell and Butterworth, 2009). Importantly, both NO and peroxynitrite inhibit α KGDH activity which further exacerbates mitochondrial dysfunction and oxidative stress (Park et al., 1999; Hazell and Butterworth, 2009). Not surprisingly, concentrations of reactive oxygen species (ROS) were found to be significantly elevated in the thalamus and cortex in the PTD model (Langlais et al., 1997). Thus, TD results in a vicious biochemical cycle wherein decreases of α KGDH catalyze excessive ROS production which further inhibits the ability of α KGDH to regulate TCA cycle turnover (Hazell and Butterworth, 2009).

Unlike in the clinical setting where individuals suffering from TD are only be monitored upon seeking medical attention, rodent models of TD allow for near-continuous monitoring and assessment. In the thiamine-deficient food model and in the PTD model, lesions limited largely to the anteroventral ventrolateral (AVVL) and ventroposterolateral (VPL) thalamic nuclei (Zhang et al, 1995) are observed <1 hr after onset of seizures and opisthotonus (spasm of the muscles causing backward arching of the head, neck and spine). Specifically, there is an approximate 35% loss of neurons within the VPL thalamus with concomitant increases in reactive astrocytes and microglia activation (Todd and Butterworth, 1998, 1999). Three to five hours after the appearance of seizures, there is massive cell loss in the midline thalamic nuclei and mammillary bodies (Zhang et al, 1995). Approximately 6–14 hr of seizures, cell death extends throughout the periaqueductal grey and tegmentum. Furthermore, hemorrhagic lesions are also observed in the hypothalamus and thalamic geniculate nuclei (medial and lateral). Interestingly, there is little evidence of neurodegeneration in the hippocampus or cortex in the PTD model (Langlais and Mair, 1990).

The pathology seen in rodent TD models largely mimic those seen in humans with WE as described by functional imaging or postmortem histology. However, human imaging studies often describe typical and atypical neuroimaging findings, (reviewed in Zuccoli and Pipitone, 2009) which likely relates to the diversity of clinical presentations of individuals with WE as well as whether or not the patient is an alcoholic (Zuccoli and Pipitone, 2009; Zuccoli et al., 2009, 2010b). Typical neuroimaging findings are present in the mammillary bodies, periaqueductal grey, and a number of thalamic nuclei including dorsomedial, anterior, pulvinar, and midline nuclei. In contrast, atypical neuroimaging findings of WE include signal intensity changes in regions such as cerebellum, caudate, and cerebral cortex (Lapergue et al., 2006; reviewed in Zuccoli and Pipitone, 2009). Signal intensity changes in the basal ganglia have typically only been observed in pediatric cases of WE (Zuccoli et al., 2010c) but were recently reported in two adult cases (Zuccoli et al., 2010a). Only recently have magnetic resonance imaging (MRI) methods been applied to the study of TD in rodent models. A comparison between results from human neuroimaging studies and those using rodent models of TD is shown in Table 2. An advantage of rodent models of TD is the reproducibility and reduced variability in the resultant brain and behavioral pathology. In a recent study in PTD-treated rats, regions showing signal intensity increases in T2-weighted MRI included the neocortical white matter, tectum, cerebellar peduncles, as well as anterior, dorsal, and midline thalamic nuclei and during the early acute (WE) phase (Dror et al., 2010). No changes were observed in the basal ganglia in two MRI studies of PTD treated-rats (Pfefferbaum et al., 2007; Dror et al., 2010). As shown in Table 2, these neuroimaging data resemble many, but not all, of that seen in individuals with WE.

Neurochemical Changes—Rodent models have been influential in describing the neurochemical changes in the TD brain. All major neurotransmitter systems are altered during the acute stage of TD, including transmitter synthesis and/or release mechanisms. Selective regions of the thalamus, such as the midline and lateral posterior nuclei, demonstrate increased extracellular glutamate levels 4–5 hours after the onset of seizures

(see below) which suggests that thalamic lesions seen in the PTD model may result from excitotoxicity (Hazell et al., 1993; Langlais and Zhang, 1993; Todd and Butterworth, 1998). Mechanistically, increased glutamate levels during TD might be a consequence of impaired glutamate buffering by the astrocytic transporters *GLT1* and *GLAST* (Hazell et al., 2001) and/or increased presynaptic transmission of glutamate via pathological reductions of complexin I and II (Hazell and Wang, 2005). These findings are also consistent with impaired mitochondrial oxidation as increased oxidative stress is known to inhibit glutamate transport via peroxynitrite-induced transporter breakdown (Volterra et al., 1994; Trotti et al., 1996, 1998). Increased glutamate levels may play a role in seizure generation observed during the acute stages of TD in rodent models.

Gamma-aminobutyric acid (GABA) activity is reduced during the acute phase of TD in rodent models (Thompson and McGeer, 1985; Heroux and Butterworth, 1988). This might be due to impaired TCA cycle turnover as reduced *de novo* synthesis of GABA is seen in the medial thalamus of PTD-treated rats (Navarro et al., 2008). Deficits of C-glucose incorporation into GABA and glutamate have also been observed (Gaitonde et al., 1974, 1975). Thus, the altered balance of GABA and glutamate levels in the brain may be responsible for the seizures observed during the acute stages of TD in rodent models.

TD alters norepinephrine (NE) and dopamine (DA) levels, which might result from vesicular dysfunction via impaired catecholamine metabolism (Mousseau et al., 1996). In the frontal cortex, hypothalamus, and thalamus of PTD-treated rats, impaired vesicular transport leads to intracellular release and breakdown of DA (Mousseau et al., 1996). This may lead to a reduction in synaptic/extracellular release of DA and may blunt NE production through impaired metabolic function.

As described above, TD results in a reduction of TPP activity as well as decreases in another TPP-dependent enzyme, pyruvate dehydrogenase (Gibson et al., 1982; Pekovich et al., 1998). This enzyme is critical for the synthesis of acetyl-CoA from pyruvate during glycolysis (Butterworth, 1993a; Todd & Butterworth, 1999). The TD-induced decrease in levels of acetyl-CoA (Jankowska-Kulawy et al., 2010), which is a critical co-factor of acetylcholine (ACh), consequently results in a decrease ACh synthesis (Gibson et al., 1984). These data combined with the documented neurodegeneration of cholinergic neurons after chronic TD or PTD treatment (see below) reflect major changes in ACh function both during and after TD.

Dorsal and medial raphe neurons show reduced levels of tryptophan hydroxylase in mice fed a thiamine-free diet for 20 days (Nakagawasai et al., 2007), indicative of impaired synthesis of serotonin (5-HT). Interestingly, head-twitch responses in TD mice elicited by intracerebroventricular administration of a 5-HT_{2A} receptor agonist is enhanced, suggesting that TD alters the function of 5-HT_{2A} receptors (Nakagawasai et al., 2007). In the PTD rat model, increased 5-HT synthesis has been observed in the cerebellum, hippocampus, striatum, hypothalamus and cortex after administration of a monoamine oxidase inhibitor (Van Woert et al., 1979). These neurochemical effects as well as behavioral manifestations of TD are completely reversed within two hours after thiamine administration (Van Woert et al., 1979).

There is also evidence that histamine is a key mediator of cell death in the acute TD brain (Steinbusch and Verhofstad, 1986; Langlais et al., 2002). Altered levels of histamine have been observed in brain regions vulnerable to neurodegeneration in PTD-treated rats (Langlais et al., 1994; McRee et al., 2000). Moreover, Langlais and colleagues (2002) demonstrated that therapeutic depletion of brain histamine levels prior to TD symptom onset was capable of attenuating thalamic neurodegeneration in the PTD model. While these

findings suggest an integral role for histamine in the pathogenesis of TD, the exact mechanisms remain unknown. Histamine may influence TD-induced neurodegeneration by increasing blood-brain barrier permeability (Steinbusch and Verhofstad, 1986), glutamate-related excitotoxicity (Colwell and Levine, 1997; Shelton and McCarthy, 2000) and/or proinflammatory cytokine release (Abbot, 2000). Further research is needed to elucidate the role of histamine in the neuropathology associated with TD.

Behavioral Changes—In addition to (or instead of) the cardinal symptoms described above, patients with WE can present with a diverse number of symptoms which may also vary depending on the age of the affected individual (Kornreich et al., 2005; Fattal-Valevski et al. 2009; Sechi et al. 2007; Sugai and Kikugawa, 2010). Some of presenting symptoms of individuals with TD have not been directly assessed in rodent models of TD such as apnea, hearing loss, and dysarthria. Nevertheless, several behavioral comparisons between TD in rodents and humans are available and are described below.

A number of abnormal behaviors are observed once rodents reach TD status. However, the temporal progression of behavioral change differs between the thiamine-free diet model and the PTD model. In the thiamine-free diet model (no PTD), mice display performance deficits in the Y-maze as early as 9 days after the start of treatment (Zhao et al., 2008). In this same model, rats display an increase in startle response along with bradycardia, lack of appetite, and hypothermia after 14 days of treatment (Onodera et al., 1981, 1991; reviewed in Nakagawasai, 2005). As the TD state progresses (day 25) in the thiamine-free diet model, there is memory impairment on tasks such as passive avoidance (Nakagawasai et al., 2001) and changes in emotional behavior, including increased muricide and impairment on the forced swim task (Nakagawasai et al., 2001). Once these behavioral symptoms develop, they are not suppressed by the administration of thiamine, indicative of a significant change in brain physiology and neurochemistry (Nakagawasai, 2005). Interestingly, some 5-HT and NE reuptake inhibitors can decrease some of the observed emotional behavior changes of acute TD (Onodera et al., 1981; Nakagawasai et al., 2001).

In contrast to the thiamine-free diet model, PTD treatment generally lasts for approximately 16 days, at which point seizures and opisthotonus begin and continue until death unless parenteral thiamine is administered in order to begin restoration of thiamine levels. The first behavioral symptoms of the PTD model include weight loss which becomes evident approximately on day 10 of PTD treatment followed by ataxia between days 13–15 of treatment (Zhang et al., 1995). Within 1–2 days of the development of ataxia, PTD-treated rats display a loss of righting reflex and the emergence of seizures and opisthotonus (day 16–17; Zhang et al., 1995). These later symptoms are associated with significant brain lesion and the degree and extent of neural injury is directly related to when parenteral thiamine treatment is administered (typically 2 doses of 100 mg/kg i.p. of thiamine hydrochloride; Anzalone et al. 2010).

II. Cytopathological, Neurochemical and Behavioral Changes Following Recovery from Thiamine Deficiency in the PTD model

The PTD model has been the most widely used in the examination of brain and behavior changes after recovery from TD, and is an accepted model of WKS. The approach generally used in our lab and others is to continue PTD treatment until behavioral manifestations of TD appear such as seizures (~16 days). Upon the onset of seizures, parenteral thiamine is administered to prevent death and begin the TD recovery process. Therefore, unlike in most clinical scenarios where affected individuals seek medical attention and receive treatment at varying times after the onset of TD symptoms, the PTD model allows for very stereotyped and reproducible effects. Studies using this approach with the PTD model have revealed

numerous neuroanatomical, neurochemical, and behavioral changes that persist from weeks to months as well as others which are likely permanent. In the following sections, we review these neurobiological changes and their relevance to behavioral dysfunction following recovery from TD with particular emphasis on the memory deficits observed in WKS.

Cytopathology

i. Subcortical Pathology in PTD: Following PTD treatment and recovery from TD, hallmark neuropathology is observed in multiple thalamic nuclei (anterior, medial dorsal, intralaminar [ILn], posterior) similar to that seen in WKS patients. In addition to cell loss, there is evidence of hemorrhaging, neural atrophy, and intense gliosis (Mair et al., 1988). As shown in Figure 1, there is a significant loss of neurons in the anterior nuclei and ILn as well as the medial mammillary nuclei (Langlais and Savage, 1995). Much like what has been described in individuals with WKS (Victor et al., 1989), the PTD model produces degeneration of key limbic system fiber tracts such as the mamillothalamic tract and fornix (Markowitsch, 1988; Langlais and Zhang, 1997). Together, these diencephalic structures constitute integral components of the limbic-forebrain memory system and disruption of this circuit following TD is strongly associated with the amnesic phenotype of WKS (discussed below).

A number of studies have attempted to relate the amnesic symptoms of WKS with damage to specific thalamic regions, especially the anterior nuclei, medial nuclei, and ILn complex (Mair et al., 1979; Mayes et al., 1988; Harding et al., 2000). Following postmortem histological analyses, Harding and colleagues found that the extent of damage to the anterior nuclei predicted the degree of memory impairments in chronic alcoholics with WKS (Harding et al., 2000). Using this same approach of postmortem analyses of alcoholics with and without memory deficits, damage to subcortical structures including the hypothalamus (Harding et al., 1996), brainstem serotonergic nuclei (Halliday et al., 1993), the noradrenergic locus coeruleus (Halliday et al., 1992), basal forebrain (Cullen et al., 1997) and the hippocampus (Harding et al., 1997) were found to be uncorrelated with the clinical presentation of memory impairments. In contrast, Gold and Squire (2006) reported similar amnesic profiles in three patients that had lesions to one of three different limbic regions including the hippocampus, ILn/internal medullary lamina (IML), or anterior thalamus. Comparisons between postmortem (Cullen et al., 1997; Halliday et al., 1992, 1993) and functional neuroimaging (Gold and Squire 2006) are difficult but suggest that the thalamus and hippocampus are part of a *limbic-diencephalic memory circuit* and that damage to a single component of this circuit is sufficient to disrupt memory functioning (see also Aggleton and Brown, 1999).

Brain damage in humans with TD is seldom restricted to individual thalamic nuclei leading researchers to rely on animal lesion studies to further identify the individual contributions of specific brain nuclei to memory function and memory dysfunction in WKS. For example, selective damage to the anterior thalamic nuclei in rodents produces impairments in both working and reference forms of spatial memory (Mitchell and Dalrymple-Alford, 2005), a result likely due to the strong reciprocal connectivity of these nuclei with the hippocampus (Gabriel and Sparenborg, 1986; Gabriel et al., 1987; van Groen and Wyss, 1995). The underlying mechanisms of spatial memory deficits associated with anterior thalamic lesions remains to be clarified, but might involve: 1] failed spatial information storage (Bryatt and Dalrymple-Alford, 1996; Warburton and Aggleton, 1999; Warburton et al., 2000), 2] perturbed thalamic theta activity (Vertes et al., 2001) and/or 3] a loss of thalamic head direction cells (Aggleton and Brown, 1999; Taube and Bassett, 2003). These data are relevant toward a greater understanding of how anterior thalamic lesions in individuals with WKS results in memory deficits (discussed below).

Lesions of the ILn/IML complex, especially the rostral component (i.e., central median, paracentral, and central lateral nuclei), are observed in the PTD model of TD. These nuclei are proposed to be involved in attentional processes that can modulate working memory performance such as short-term shifting and sustained attention, (Van der Werf et al., 2000, 2002; Schiff, 2008). Consistent with a role in attention, rats with ILn/IML lesions do not show improvements on a signal-detection task when the inter-trial interval is increased, compared to control rats that do show improved performance (Newman and Burk, 2005). Thus, the primary results of ILn/IML lesions appear to relate to attentional deficits that contribute to working memory impairment. In support of these conclusions are data from a recent human functional magnetic resonance imaging (fMRI) study that demonstrated increased signal intensity of the thalamus with increases in working memory or visual attention load (Tomasi et al., 2007). These data and those described above, point to separate roles played by anterior thalamus and ILn/IML lesions in the cognitive phenotype of WKS.

Neuronal loss is observed in the medial dorsal nucleus of the thalamus in the PTD model of WKS (LaRoche et al. 1987). Unlike lesion to other regions of the thalamus such as the anterior nuclei, damage to the medial dorsal thalamus in rats and nonhuman primates has little effect on spatial memory (Neave et al. 1993). Instead, lesion of medial dorsal nuclei has been observed to impair memory for reward location (Mitchell and Dalrymple-Alford, 2005) as well as the acquisition and expression of reward-guided behaviors (Yu et al., 2010) in rats. In nonhuman primates lesions of the mediodorsal thalamus have been shown to impair reward-based decision making on simple discrimination tasks (Gaffan and Murray, 1990) as well as in reward-devaluation studies (Mitchell et al. 2007; Izquierdo and Murray, 2010). Interestingly, the mediodorsal thalamus receives projections from the amygdala (Aggleton and Mishkin, 1984) and amygdala lesions produce similar behavioral deficits to that seen after mediodorsal lesions (Izquierdo and Murray, 2010), suggesting that the medial dorsal thalamus is part of the *extended-amygdala* system that is critical for reward-based decision making. These data point to a distinct role played by the medial dorsal thalamus in processing reward-related information compared to the anterior nuclei or the ILn which participate more in spatial memory and attention, respectively (described above). Thus, these different thalamic nuclei are critical components of different learning/memory, reward, and attentional systems in the intact brain and each contribute to the cognitive deficits observed in WKS.

Findings of structural damage to the hippocampus in WKS patients has been mixed (Caulo et al., 2005; Mair, 1994; Harding et al., 1997). Similarly, early reports on the structural integrity of the hippocampal formation following PTD treatment revealed no neuropathology (Langlais et al., 1992). However, recent *in vivo* MRI animal studies have revealed some hippocampal shrinkage following PTD treatment (Pfefferbaum et al., 2007). Despite equivocal anatomical findings, there is good evidence of hippocampal dysfunction in both human and rodents after TD. For example, studies from our laboratory (Roland et al., 2007; Savage et al., 2003, 2007; Vetreno et al., 2008) indicate that acetylcholine release in the hippocampus is reduced in PTD rats during spatial navigation and is accompanied by spatial memory deficits. Likewise, an fMRI study with WKS patients revealed reduced activation of the hippocampus during both the encoding or recognition phases of a visual matching-to-sample task despite no observed structural damage to the hippocampus of these patients (Caulo et al., 2005). These data in humans and rodent models suggest that hippocampal dysfunction seen after TD may be due to damage to structures functionally connected with the hippocampus.

The basal forebrain is vulnerable to TD-induced neurodegeneration. Cell death and dendritic reorganization in the nucleus basalis (nBM) as well as the medial septum (MS) and vertical limb of the diagonal band (DB) was reported in postmortem analyses of WKS brains

(Arendt et al., 1995). Studies using TD rodent models have reported similar neurodegeneration. In particular, a 30% reduction in choline acetyltransferase (ChAT) immunopositive neurons (Pitkin and Savage, 2001; 2004) was observed in the MS/DB of PTD-treated rats and this cell loss was correlated with the degree of memory impairment (Roland and Savage, 2009b). Consistent with a loss of MS/DB ChAT neurons, there is also a loss of cholinergic fibers in the cortex (Anzalone et al., 2010) and hippocampus (Nakagawasai et al., 2000) of PTD-treated rats. Moreover, *in vivo* microdialysis studies with the PTD model have demonstrated reduced ACh activity in the hippocampus and cortex (Savage et al., 2003; Roland and Savage, 2007; Savage et al., 2007; Vetreno et al., 2008). Thus, loss of basal forebrain cholinergic projection neurons likely contributes to the decline in hippocampal function and memory impairments in individuals with WKS as well as in the PTD model.

ii. Cortical and White Matter Pathology in PTD: While contributions of diencephalic structures to the amnesic condition associated with WKS have been extensively studied (Langlais et al., 1996; Mair, 1994), cortical and white matter neuropathology has received less attention. Histopathological (Krill et al., 1997) and *in vivo* neuroimaging (Colchester et al., 2001; Jernigan et al., 1991) studies of humans with WKS have revealed significant tissue shrinkage of the neocortex including temporal, orbitofrontal, frontal and parietal cortices. Similarly, PTD treatment culminates in degeneration of the frontal, parietal and retrosplenial cortices consisting of axonal and terminal atrophy and cortical thinning due to laminar specific (i.e., layers III and IV) cellular degeneration (LaRoche et al., 1987; Langlais and Zhang, 1997). Pires and colleagues (2001, 2005) demonstrated a reduction in acetylcholinesterase (AChE) activity in the neocortex of TD rats. Work by our group has also revealed a reduction in AChE-stained fibers in the cortex of PTD rats; the extent of AChE fiber loss was correlated with deficits in memory performance (Vetreno et al., 2010). Therefore, cortical ACh dysfunction may occur as a consequence of a loss of basal forebrain cholinergic cells (described above) and may underlie some of the cognitive impairments common in the PTD model and WKS.

Selective white matter loss in the frontal and parietal cortices is common (Krill et al., 1997) as is a reduction in the size of the corpus callosum in alcoholics with WE (Lee et al., 2005). Similar cortical and callosal white matter loss is observed in the PTD model along with degeneration of the anterior commissure as well as external and internal capsules (Langlais and Zhang, 1997). Finally, thinning of myelin sheaths and reduced axon thickness occur in the corpus callosum of a rat TD model (He et al., 2007).

iii. Cerebellum, Midbrain and Brainstem Pathology in PTD: Neuroimaging (Sullivan et al., 2000; reviewed in Sullivan and Pfefferbaum, 2009) and postmortem (Baker et al., 1999) studies of alcoholics with WKS have revealed reductions in grey and white matter of the cerebellum including a reduction in the number of Purkinje cells in the vermis in individuals with WKS (Butterworth, 1993b). Pathological changes associated with WKS have also been reported to occur in the periaqueductal grey, superior and inferior colliculus, trochlear nucleus, and tegmental and pretectal regions of the human midbrain (Victor et al., 1989; Krill, 1996). Similar midbrain pathology is observed in rodents TD models (Troncoso et al., 1981; Irle and Markowitsch, 1982; Aikawa et al., 1984; Pfefferbaum et al., 2007). Pontine edema, especially within the superior and inferior vestibular nuclei, has also been reported both in individuals with alcoholism-associated WKS (Sullivan and Pfefferbaum, 2001) as well as in the PTD model (Takahashi et al., 1988; Watanabe and Kanabe, 1978). In particular, the superior and lateral pontine vestibular nuclei are damaged following PTD treatment, as are the medullary inferior olives (Troncoso et al., 1981). Damage to these structures likely contributes to symptoms like ataxia seen in humans with WKS as well as

the PTD model. Further research is required to delineate the contributions of these brain regions to the diverse pathological profile of TD.

Neurochemical Changes

i. Amino Acids: Long-term neurochemical alterations have been reported in the PTD model 1–4 months after the restoration of thiamine levels. First, there are significant reductions in overall GABA and glutamate levels in the medial thalamus (Langlais et al., 1988). In addition, the amnesic effects of the glutamate antagonist MK-801 are increased four weeks after recovery from TD, indicative of disturbances in glutamatergic signaling (Savage et al., 1999). Carvalho and colleagues (2006) showed that 16-weeks after recovery from TD, rats were impaired on a water maze task and demonstrated reduced glutamate uptake in the prefrontal cortex (PFC). This is similar to the hypoactivity of PFC and impaired performance on memory and executive function tasks reported in fMRI studies of individuals with WKS (Paller et al., 1997; Reed et al., 2003; Caulo et al., 2005). Together these data strongly point to long-term alterations in glutamatergic function after TD.

Decreases in thalamic GABA levels have been reported soon after recovery from TD in the PTD model (3-days; Heroux and Butterworth, 1988). Similar reduction in GABA levels in the thalamus was observed 9 weeks after recovery from TD in the same model (Langlais et al., 1988). These observations suggest permanent alterations in the synthesis and/or utilization of both GABA and glutamate (described above) within the thalamus. Alterations in the balance between glutamate and GABA likely result in excitability changes within the thalamus, as well as signaling to thalamic efferents (i.e. thalamocortical projections), and processing of thalamic afferents (i.e. corticothalamic projections).

ii. Acetylcholine: Deficits in cholinergic function have been implicated in the long-term cognitive and behavioral impairments associated with WKS as well as the memory deficits seen in the PTD model (Savage et al., 2003; Pires et al., 2005; Savage et al., 2007; Roland et al., 2008). For example, one month after recovery from TD in the PTD model, rats display reduced hippocampal ACh efflux that is correlated with impaired behavioral performance on a spontaneous alternation task (Savage et al., 2003, 2007; Vetreno et al., 2008) and a delayed matching-to-sample task (Roland and Savage, 2007). Similar associations between impaired behavioral performance and reduced ACh efflux have been detected in other brain areas including the frontal cortex and retrosplenial cortex (Pires et al., 2005; Anzalone et al., 2010) suggesting widespread dysfunction of forebrain cholinergic activity. Pires and colleagues (2005) reported decreased levels of AChE activity in the cortex both during and after recovery from TD (3-months) in PTD-treated animals as well as reduced ACh release from cortical slices (Pires et al., 2001, 2005). Furthermore, PTD-induced decreases in the cortex were associated with learning impairments on spatial memory tasks such as the Morris water maze (MWM), suggesting that cortical ACh activity plays an important role in spatial learning (Pires et al., 2005). Interestingly, in the PTD model, ACh release is unaffected in other brain regions outside of the hippocampus and cortex such as the striatum (Vetreno et al., 2008) and amygdala (Savage et al., 2007).

Consistent with the role of cortical and hippocampal ACh in memory, administration of AChE inhibitors or herbal compounds that increase ACh release can rescue the cognitive performance deficits observed on tasks such as passive avoidance, water maze, and non-matching-to position after recovery from TD in rats (Nakagawasai, 2005; Roland et al., 2008). Reversal of memory deficits can also be achieved via blockade of GABA receptors in the medial septal region and suggests that balancing ACh and GABA levels in the septohippocampal circuit may prove to be an effective therapeutic approach for the treatment of cognitive impairments of TD in rodent models and potentially an avenue for the development of future pharmacological treatment of individuals with WKS.

iii. Monoamines: Reductions of NE metabolites in the cerebral spinal fluid of WKS patients are correlated with cognitive deficits (McEntee and Mair, 1978) and can be reversed by administration of α -adrenoreceptor agonists (McEntee and Mair, 1980; Mair and McEntee, 1986). Similarly, neurochemical analysis of PTD brains revealed long-term (13–15 weeks after TD) decreases in NE levels in the cortex and olfactory bulbs, with surprising increases in NE levels in the cerebellum (Mair et al., 1985; Langlais et al., 1987). To reconcile these disparate findings, it has been posited that cortical NE deficits may reflect select degeneration of long-range projection fibers from the locus coeruleus, whereas increased NE content in the cerebellum is produced via sprouting of proximal cerebellar afferents (Langlais et al., 1987).

Change in serotonin activity and its relation to memory impairment in WKS is not well understood. Although there is evidence for the loss of serotonergic neurons in the raphe nucleus of WKS patients (Halliday et al., 1993; Baker et al., 1996), there are limited case studies that document the recovery of cognitive performance following drug therapy with serotonin reuptake inhibitors (Numata, et al., 2005). In the PTD model, there is also a loss of serotonergic neurons in the raphe nucleus (Matsushita et al., 1999) but increases in serotonin and/or its metabolites in the thalamus and striatum following recovery from TD (Langlais et al., 1987, 1988; Vigil et al., 2010). A recent study demonstrated moderate correlation between high levels of the serotonin metabolite 5-hydroxyindolacetic acid in the thalamus and spatial memory performance on the MWM (Vigil et al., 2010). Such results suggest that altered serotonin levels may contribute to cognitive dysfunction associated with TD.

In conclusion, during the acute stages of TD as well as after recovery from TD there are significant changes in a number of neurotransmitters systems. Moreover, several neurochemical changes have been shown to correlate with cognitive deficits observed in both humans with WKS as well as animal models (Anzalone et al., 2010; Mair and McEntee., 1986; McEntee and Mair, 1978, 1980; Roland and Savage, 2009; Savage et al., 2003; Vigil et al., 2010). There is emerging evidence that restoring NE or ACh levels can lead to improved cognitive outcomes in WKS patients and TD animal models (Cochrane et al., 2005; Iga et al., 2001; McEntee and Mair, 1980; Roland et al., 2009, 2010) which are relevant to future design of therapies for individuals with WKS.

Behavioral Changes—After recovery from TD (1–12 months), studies using the PTD model have consistently demonstrated deficits on working memory tasks that are dependent on hippocampal function such as spatial matching-to-position (MTP) and nonmatching-to-position (NMTP). Impaired spatial memory and navigation on tasks such as the MWM and the radial arm maze are also observed. In particular, PTD-treated rats exhibit longer latencies to reach the hidden platform and demonstrate increased thigmotaxic searching behavior (circling the rim of the maze; Langlais et al., 1992) on the MWM which is similar to the type of memory deficits observed after experimental hippocampal lesion (Morris et al., 1982). In the radial arm maze task, PTD-treated rats show significant deficits in working memory for maze arms baited with food compared to modest reference memory impairments for unbaited maze arms (Robinson and Mair, 1992). In the radial-arm maze task, memory for baited arms is thought to model human episodic/declarative memory. In contrast, memory for unbaited arms is thought to model reference/non-declarative memory. Thus, the PTD model demonstrates greater impairment of episodic/declarative memory than reference/non-declarative, which is a behavioral finding very similar to that observed in WKS patients (see Gold & Squire, 2006; Kopelman et al., 2009). Recently, our lab has also demonstrated that PTD-treated rats are impaired on a spontaneous alternation task, a non-reinforced spatial memory task. Behavioral deficit on this task was correlated with impaired ACh release in the hippocampus (Savage et al., 2003; Savage et al., 2007; Vetreno et al., 2008) suggesting that TD results in deficits in cholinergic function in the hippocampus that

manifests in memory deficits. Thus, despite a lack of neuropathological evidence indicating hippocampal damage in the PTD model, hippocampal function is severely compromised. Consistent with results observed in rodent TD models, memory deficits in WKS patients are similar to patients with hippocampal damage (after stroke, encephalopathy, etc) despite a lack of clear evidence of pathological damage to the hippocampus of WKS patients. Therefore, we posit that memory dysfunction in WKS stems from lesion to the thalamus (reviewed above) as well as loss of hippocampal cholinergic function.

Damage to midline thalamic nuclei is a key predictor of working memory impairment in the PTD model (Knoth and Mair, 1991; Mair et al., 1991; Langlais et al., 1992, Langlais and Savage, 1995; Mumby et al., 1999; Roland and Savage, 2007) as well as other diencephalic regions, such as the anterior thalamus and mammillary bodies (Langlais and Savage, 1995; Savage et al., 1997). However, not all memory function is altered by TD in the PTD model. For example, similar to WKS patients, there are some learning and memory tasks on which PTD-treated rats show preserved performance. These include simple discrimination tasks that are not dependent on hippocampal function such as light-dark (Mair et al., 1988) or left-right discrimination tasks (Vetreno et al., 2008). In contrast, performance is impaired on an object-based, delayed nonmatch to sample discrimination task in WKS patients (Squire et al., 1988) as well as after PTD treatment in nonhuman primates (Witt and Goldman-Rakic, 1983) and rats (Mumby et al. 1995). These effects are thought to be mediated by thalamic lesions caused by TD.

We recently found that during learning of a left-right discrimination task, there was reduced hippocampal but increased striatal release of ACh in the in PTD-treated rats compared to controls (Vetreno et al., 2008), suggesting that procedural memory systems display increased ACh activity in the face of pathological decreases in hippocampal ACh activity (described above). Similarly, we have found that there is no deficit when PTD-treated rats are trained using a Pavlovian procedure that pairs unique rewards (rat chow vs. chocolate milk) in a MTP task. More specifically, both PTD-treated and control rats are able to learn this version of the task in about 100 trials (Langlais and Savage, 1995). In contrast, without specific task-dependent reward pairing, PTD-treated rats require twice as many trials to learn the MTP task than control rats. Therefore, training protocols that incorporate Pavlovian-based learning reverse the effects of TD, suggesting that these cognitive demands recruit neural circuits that are resistant to TD-induced brain injury (Savage and Ramos, 2009). These data are important toward the development of behavioral learning approaches and strategies for use with individuals with WKS.

In addition to the anterograde memory deficits, individuals with WKS display retrograde memory loss - the inability to recall information learned prior to brain insult. Moreover, the hallmark feature of retrograde amnesia in WKS patients is that it is temporally graded; memory loss is greater for events that occurred immediately preceding brain damage whereas memory for events that occurred well-before the brain injury remains intact. In rodent models such as the PTD model, retrograde memory can be assessed by retesting animals on a task that was learned prior to PTD-treatment. Using this approach with the MWM, PTD rats re-tested after treatment did not display any deficits (Langlais et al., 1992; Pires et al., 2005). Lack of retrograde amnesia following PTD treatment was also reported on an object discrimination task (Mumby et al., 1999). Furthermore, pre-training rats prior to PTD treatment did not impair retrograde memory on a passive avoidance task (Langlais and Savage, 1995). This lack of retrograde memory loss was also reported in rats following electrolytic lesion to the midline thalamic nuclei (Langlais et al., 1992). Thus, although the PTD model recapitulates the anterograde memory impairment seen in WKS, to date, TD in rodents has not been shown to produce retrograde memory loss. Thus, rodent models of TD may not produce sufficient hippocampal dysfunction to create retrograde amnesia as is

observed in humans. Alternatively, task-specific features used to measure cognitive performance in rodents such as the amount of training or the interval between learning, brain injury and retesting are not optimal for revealing retrograde amnesia (see Sutherland et al., 2010). Further investigation is needed to understand these differences between TD-induced retrograde memory deficits in humans and rodent models.

Concluding Remarks

Early understanding of human memory was derived from postmortem observation of human brain damage associated with symptoms of memory impairment. The seminal works of Wernicke (Thomson et al., 2008) and Korsakoff (1889) on cognitive impairment associated with TD not only provided insight into TD-induced brain pathology, but were also the impetus for the discovery of multiple memory systems within the brain. More recent technologies such as fMRI and positron emission tomography have allowed physicians and scientists to examine both structural and functional changes that occur in individuals with WE and WKS. Animal models, however, have allowed for the precise description of neurochemical changes that occur in particular brain regions both during and after recovery from TD. Together, these approaches have provided greater understanding of the cellular mechanisms, neuropathology, and clinical profiles of WE and WKS.

The PTD model of WKS has permitted greater understanding of brain structures involved in learning and memory deficits characteristic of WKS. Work from our laboratory employing the PTD model has identified hippocampal hypofunction as a major factor contributing to the cognitive impairments associated with TD despite a lack of gross anatomical pathology in the hippocampus compared to the thalamus and mamillary bodies (Roland and Savage, 2007; Savage et al., 2003; Vetreno et al., 2008). Work from our group (Pitkin and Savage, 2001, 2004; Roland and Savage, 2009b) and others (Arendt et al., 1995) has revealed a compromised basal forebrain cholinergic system as causal to hippocampal cholinergic dysfunction in the PTD model, an effect demonstrated by neurodegeneration of basal forebrain cholinergic neurons as well as reduced hippocampal ACh efflux *in vivo*. Future studies are necessary to understand why cholinergic neurons of the medial septum but not nucleus basalis are vulnerable to TD-induced degeneration (Savage et al., 2007) and to determine methods to protect these neurons at the earliest stages of injury.

A number of areas merit further exploration toward greater understanding of the relationship between brain and behavioral changes seen after TD. For example, recent work has demonstrated reductions in postnatal neurogenesis in the dentate gyrus in a TD rodent model (Zhao et al., 2008). Therefore, further research into the cellular consequences of TD is required to elucidate the potential involvement of reduced neurogenesis in cognitive dysfunction associated with TD. In light of the fact that numerous pharmacological and behavioral methods have been identified to increase neurogenesis in the rodent dentate gyrus such as following fluoxetine administration (Malberg et al., 2000) or voluntary exercise (van Praag et al., 2003), there is the potential to test the effect of these neurogenesis-stimulating treatments in the PTD model.

Although TD-induced deficits of cognition have been generally emphasized in both clinical studies and those using rodent models, less attention has been paid to those cognitive faculties that remain intact after TD. Using the PTD model, we have demonstrated preserved functional memory systems of the amygdala and striatum as well as increased ACh release in the striatum compared to controls (Vetreno et al., 2008). Future studies must focus greater attention toward understanding of the plastic brain changes that emerge after TD as they relate to learning and memory function and dysfunction.

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

References

- Abbott NJ. Inflammatory mediators and modulation of blood brain barrier permeability. *Cell Mol Neurobiol.* 2000; 20:131–147. [PubMed: 10696506]
- Agabio R. Thiamine administration in alcohol-dependent patients. *Alcohol Alcohol.* 2005; 40(2):155–6. [PubMed: 15550446]
- Aggleton JP, Brown MW. Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *Behav Brain Sci.* 1999; 22:425–444. [PubMed: 11301518]
- Aggleton JP, Mishkin M. Projections of the amygdala to the thalamus in the cynomolgus monkey. *J Comp Neurol.* 1984; 222:56–68. [PubMed: 6321564]
- Aikawa H, Watanabe IS, Furuse T, Iwasaki Y, Satoyosho E, Sumi T, Moroji T. Low energy levels in thiamine-deficient encephalopathy. *J Neuropathol Exp Neurol.* 1984; 43:276–287. [PubMed: 6726285]

- Anzalone S, Vetreno RP, Ramos RL, Savage LM. Cortical cholinergic abnormalities contribute to the amnesic state induced by pyridoxamine-induced thiamine deficiency in the rat. *Eur J Neurosci.* 2010; 32(5):847–858. [PubMed: 20726882]
- Arendt T, Bruckner MA, Bigl V, Marcova L. Dendritic reorganization in the basal forebrain under degenerative conditions and its defects in Alzheimer's disease. II Aging, Korsakoff's disease, Parkinson's disease, and Alzheimer's disease. *J Comp Neurol.* 1995; 351:189–222. [PubMed: 7535318]
- Baker KG, Halliday GM, Kril JJ, Harper CG. Chronic alcoholism in the absence of Wernicke-Korsakoff syndrome and cirrhosis does not result in the loss of serotonergic neurons from the median raphe nucleus. *Metab Brain Dis.* 1996; 11:217–27. [PubMed: 8869942]
- Baker K, Harding A, Halliday G, Kril JJ, Harper C. Neuronal loss in functional zones of the cerebellum of chronic alcoholics with and without Wernicke's encephalopathy. *Neuroscience.* 1999; 91:429–438. [PubMed: 10366000]
- Bryatt G, Dalrymple-Alford JC. Both anteromedial and anteroventral thalamic lesions impair radial-maze learning in rats. *Behav Neurosci.* 1996; 110:1335–1348. [PubMed: 8986336]
- Butterworth RF. Pathophysiologic mechanisms responsible for the reversible (thiamine-responsive) and irreversible (thiamine non-responsive) neurological symptoms of Wernicke's encephalopathy. *Drug and Alcohol Review.* 1993a; 12:315–322. [PubMed: 16840290]
- Butterworth RF. Pathophysiology of cerebellar dysfunction in Wernicke-Korsakoff syndrome. *Can J Neurol Sci.* 1993b; 20(3):S123–6. [PubMed: 8334588]
- Butterworth RF. Cerebral thiamine-dependent enzyme changes in experimental Wernicke's encephalopathy. *Metab Brain Dis.* 1986; 1:165–175. [PubMed: 3334065]
- Butterworth RF, Giguire JF, Besnard AM. Activities of thiamine-dependent enzymes in two experimental models of thiamine-deficiency encephalopathy. 2 a-ketoglutarate dehydrogenase. *Neurochem Res.* 1986; 11:567–577. [PubMed: 3724963]
- Butterworth RF, Kril JJ, Harper C. Thiamine-dependent enzyme changes in brain of alcoholics: Relationship to Wernicke-Korsakoff syndrome. *Alcohol Clin Exp Res.* 1993; 17:1084–1088. [PubMed: 8279670]
- Calingasan NY, Gibson GE. Vascular endothelium is a site of free radical production and inflammation in areas of neuronal loss in thiamine-deficient brain. *Ann N Y Acad Sci.* 2000a; 903:353–356. [PubMed: 10818525]
- Calingasan NY, Gibson GE. Dietary restriction attenuates the neuronal loss, induction of hemeoxygenase-1 and blood barrier breakdown induced by impaired oxidative metabolism. *Brain Res.* 2000b; 885:62–69. [PubMed: 11121530]
- Carvalho FM, Pereira SR, Pires RG, Ferraz VP, Romano-Silva MA, Oliveira-Silva IF, Ribeiro AM. Thiamine deficiency decreases glutamate uptake in the prefrontal cortex and impairs spatial memory performance in a water maze test. *Pharmacol Biochem Behav.* 2006; 83:481–489. [PubMed: 16687165]
- Caulo M, Van Hecke L, Toma A, Ferretti A, Tartato A, Colosimo C, Romani GL, Uncini A. Functional MRI study of diencephalic amnesia in Wernicke-Korsakoff syndrome. *Brain.* 2005; 128:1584–1594. [PubMed: 15817513]
- Cochrane M, Cochrane A, Jauhar P, Ashton E. Acetylcholinesterase inhibitors for the treatment of Wernicke-Korsakoff syndrome-three further cases show response to donepezil. *Alcohol and Alcoholism.* 2005; 40:151–154. [PubMed: 15596427]
- Colchester A, Kingsley D, Lasserson D, Kendall B, Bello F, Rush C, Stevens TG, Goodman G, Heilpern G, Stanhope N. Structural MRI volumetric analysis in patients with organic amnesia, 1: Methods and comparative findings across diagnostic groups. *J Neurol Neurosurg Psychiatr.* 2001; 71:13–22. [PubMed: 11413256]
- Caulo M, Van Hecke J, Toma L, Ferretti A, Tartaro A, Colosimo C, Romani GL, Uncini A. Functional MRI study of diencephalic amnesia in Wernicke-Korsakoff syndrome. *Brain.* 2005; 128(Pt 7): 1584–94. [PubMed: 15817513]
- Colwell CS, Levine MS. Histamine modulates NMDA-mediated swelling in the neostriatum. *Brain Res.* 1997; 766:205–212. [PubMed: 9359604]

- Cook CCH, Thomson AD. B-complex vitamins in the prophylaxis and treatment of Wernicke–Korsakoff syndrome. *British Journal of Hospital Medicine*. 1997; 57:461–465. [PubMed: 9274684]
- Cook CCH. Prevention and treatment of Wernicke–Korsakoff syndrome. *Alcohol and Alcoholism*. 2000; 35(Suppl 1):19–20.
- Coy JF, Dressler D, Wilde J, Schubert P. Mutations in the transketolase-like gene TKTL1: clinical implications for neurodegenerative diseases, diabetes and cancer. *Clin Lab*. 2005; 51(5–6):257–73. [PubMed: 15991799]
- Coy JF, Dübel S, Kioschis P, Thomas K, Micklem G, Delius H, Poustka A. Molecular cloning of tissue-specific transcripts of a transketolase-related gene: implications for the evolution of new vertebrate genes. *Genomics*. 1996 Mar 15; 32(3):309–16. [PubMed: 8838793]
- Cullen KM, Halliday GM, Caine D, Kril JJ. The nucleus basalis (CH4) in the alcoholic Wernicke–Korsakoff syndrome: Reduced cell number in both amnesic and amnesic patients. *J Neurol Neurosurg Psychiatr*. 1997; 63:315–320. [PubMed: 9328247]
- Day E, Bentham P, Callaghan R, Kuruvilla T, George S. Thiamine for Wernicke–Korsakoff syndrome in people at risk from alcohol abuse. *Cochrane Database Syst Rev*. 2004:1.
- Dror V, Eliash S, Rehavi M, Assaf Y, Biton IE, Fattal-Valevski A. Neurodegeneration in thiamine deficient rats–A longitudinal MRI study. *Brain Res*. 2010; 13(1308):176–84. [PubMed: 19857469]
- Erickson CA, Barnes CA. The neurobiology of memory changes in normal aging. *Exp Gerontol*. 2003; 38:61–69. [PubMed: 12543262]
- Fama R, March L, Sullivan EV. Disassociation of remote and anterograde memory impairment and neural correlates in alcoholic Korsakoff syndrome. *J Int Neuropsychol Soc*. 2004; 10:427–441. [PubMed: 15147600]
- Fattal-Valevski A, Bloch-Mimouni A, Kivity S, Heyman E, Brezner A, Strausberg R, Inbar D, Kramer U, Goldberg-Stern H. Epilepsy in children with infantile thiamine deficiency. *Neurology*. 2009; 73(11):828–33. [PubMed: 19571254]
- Gabriel M, Sparenborg S. Anterior thalamic discriminative neuronal responses enhanced during learning in rabbits with subicular and cingulate cortical lesions. *Brain Res*. 1986; 384:195–198. [PubMed: 3790995]
- Gabriel M, Sparenborg S, Stolar N. Hippocampal control of cingulate cortical and anterior thalamic information processing during learning in rabbits. *Exp Brain Res*. 1987; 67:131–152. [PubMed: 3622674]
- Gaffan D, Murray EA. Amygdalar interaction with the mediodorsal nucleus of the thalamus and the ventromedial prefrontal cortex in stimulus-reward associative learning in the monkey. *J Neurosci*. 1990; 10(11):3479–93. [PubMed: 2230939]
- Gaitonde MD, Fayein NA, Johnson AL. Decreased metabolism in vivo of glucose into amino acids of the brain of thiamine-deficient rats after treatment with pyriethiamine. *J Neurochem*. 1975; 24:1215–1223. [PubMed: 1127434]
- Gaitonde MK, Nixey RW, Sharman IM. The effect of deficiency of thiamine on the metabolism of (U-14C)glucose and (U-14C)ribose and the levels of amino acids in rat brain. *J Neurochem*. 1974; 22:53–61. [PubMed: 4818872]
- Gibson G, Barclay L, Blass J. The role of the cholinergic system in thiamin deficiency. *Annals of the New York Academy of Sciences*. 1982; 378:382–403. [PubMed: 7044229]
- Gibson GE, Ksiezak-Reding H, Sheu KFR, Mykityn V, Blass JP. Correlation of enzymatic, metabolic and behavioral deficits in thiamine deficiency and its reversal. *Neurochem Res*. 1984; 9:803–814. [PubMed: 6149477]
- Gibson GE, Zhang H. Interactions of oxidative stress with thiamine homeostasis promote neurodegeneration. *Neurochem Int*. 2002; 40:493–504. [PubMed: 11850106]
- Gold JJ, Squire LR. The anatomy of amnesia: Neurohistological analysis of three new cases. *Learn Mem*. 2006; 13:699–710. [PubMed: 17101872]
- Grutzendler J, Helmin K, Tsai J, Gan WB. Various dendritic abnormalities are associated with fibrillar amyloid deposits in Alzheimer’s disease. *Ann N Y Acad Sci*. 2007; 1097:30–39. [PubMed: 17413007]

- Guerrini I, Thomson AD, Cook CC, McQuillin A, Sharma V, Kopelman M, Reynolds G, Jauhar P, Harper C, Gurling HM. Direct genomic PCR sequencing of the high affinity thiamine transporter (SLC19A2) gene identifies three genetic variants in Wernicke-Korsakoff syndrome (WKS). *Am J Med Genet B Neuropsychiatr Genet.* 2005; 137B:17–19. [PubMed: 16015585]
- Halliday G, Ellis J, Harper C. The locus coeruleus and memory: a study of chronic alcoholics with and without the memory impairment of Korsakoff's psychosis. *Brain Res.* 1992; 598:33–7. [PubMed: 1486496]
- Halliday G, Ellis J, Heard R, Caine D, Harper C. Brainstem serotonergic neurons in chronic alcoholics with and without the memory impairment of Korsakoff's psychosis. *J Neuropathol Exp Neurol.* 1993; 52:567–79. [PubMed: 8229075]
- Harding AJ, Halliday GM, Ng JL, Harper CG, Kril JJ. Loss of vasopressin-immunoreactive neurons in alcoholics is dose-related and time-dependent. *Neuroscience.* 1996; 72:699–708. [PubMed: 9157316]
- Harding AJ, Wong A, Svoboda M, Kril JJ, Halliday GM. Chronic alcohol consumption does not cause hippocampal neuron loss in humans. *Hippocampus.* 1997; 7:78–87. [PubMed: 9138671]
- Harding AJ, Halliday G, Caine D, Kril JJ. Degeneration of anterior thalamic nuclei differentiates alcoholics with amnesia. *Brain.* 2000; 123:141–154. [PubMed: 10611128]
- Harper C. Thiamine (vitamin B1) deficiency and associated brain damage is still common throughout the world and prevention is simple and safe! *Eur. J Neurol.* 2006; 13:1078–1082.
- Harper CG, Giles M, Finley-Jones R. Clinical signs in the Wernicke-Korsakoff complex: A retrospective analysis of 131 cases diagnosed at necropsy. *J Neurol Neurosurg Psychiatry.* 1986; 49:341–345. [PubMed: 3701343]
- Hazell AS, Butterworth RF. Update of cell damage mechanisms in thiamine deficiency: Focus on oxidative stress, excitotoxicity and inflammation. *Alcohol Alcohol.* 2009; 44:141–147. [PubMed: 19151161]
- Hazell AS, Wang C. Downregulation of complexin I and complexin II in the medial thalamus is blocked by N-acetylcysteine in experimental Wernicke's encephalopathy. *J Neurosci Res.* 2005; 79:200–207. [PubMed: 15573404]
- Hazell AS, Butterworth RF, Hakim AM. Cerebral vulnerability is associated with selective increase in extracellular glutamate concentration in experimental thiamine deficiency. *J Neurochem.* 1993; 61:1155–1158. [PubMed: 8103080]
- Hazell AS, Rama Rao KV, Danbolt NC, Pow DV, Butterworth RF. Selective down-regulation of the astrocyte glutamate transporters GLT-1 and GLAST within the media thalamus in experimental Wernicke's encephalopathy. *J Neurochem.* 2001; 78:560–568. [PubMed: 11483659]
- He X, Sullivan EV, Stankovic RK, Harper C, Pfefferbaum A. Interaction of thiamine deficiency and voluntary alcohol consumption disrupts rat corpus callosum ultrastructure. *Neuropsychopharmacology.* 2007; 32:2207–2216. [PubMed: 17299515]
- Heroux M, Butterworth RF. Reversible alterations of cerebral α -aminobutyric acid in pyridoxamine-treated rats: Implications for the pathogenesis Wernicke's encephalopathy. *J Neurochem.* 1988; 51:1221–1226. [PubMed: 3418348]
- Heroux M, Butterworth RF. Regional alternations of thiamine phosphate esters and of thiamine diphosphate-dependent enzymes in relation to function in experimental Wernicke's Encephalopathy. *Neurochem Res.* 1995; 20:87–93. [PubMed: 7739764]
- Iga JI, Araki M, Ishimoto Y, Ohmori T. A case of Korsakoff's syndrome improved by high doses of donepezil. *Alcohol and Alcoholism.* 2001; 36:553–555. [PubMed: 11704621]
- Irle E, Markowitsch HJ. Thiamine deficiency in the cat leads to severe learning deficits and to widespread neuroanatomical damage. *Exp Brain Res.* 1982; 48:199–208. [PubMed: 7173357]
- Izquierdo A, Murray EA. Functional interaction of medial mediodorsal thalamic nucleus but not nucleus accumbens with amygdala and orbital prefrontal cortex is essential for adaptive response selection after reinforcer devaluation. *J Neurosci.* 2010; 30:661–669. [PubMed: 20071531]
- Jankowska-Kulawy A, Bielarczyk H, Pawelczyk T, Wroblewska M, Szutowicz A. Acetyl-CoA and acetylcholine metabolism in nerve terminal compartment of thiamine deficient rat brain. *J Neurochem.* 2010; 115:333–342. [PubMed: 20649840]

- Jernigan TL, Schafer K, Butters N, Cermak LS. Magnetic resonance imaging of alcoholic Korsakoff patients. *Neuropsychopharmacology*. 1991; 4:175–186. [PubMed: 2064717]
- Knott RL, Mair RG. Response latency and accuracy on a pretrained nonmatching-to-sample task in rats recovered from pyridoxamine-induced thiamine deficiency. *Behav Neurosci*. 1991; 105:375–385. [PubMed: 1907458]
- Kono S, Miyajima H, Yoshida K, Togawa A, Shirakawa K, Suzuki H. Mutations in a thiamine-transporter gene and Wernicke's-like encephalopathy. *N Engl J Med*. 2009; 360:1792–1794. [PubMed: 19387023]
- Kopelman MD, Thomson AD, Guerrini I, Marshall EJ. The Korsakoff syndrome: Clinical aspects, psychology and treatment. *Alcohol Alcohol*. 2009; 44:148–54. [PubMed: 19151162]
- Kornreich L, Bron-Harlev E, Hoffmann C, Schwarz M, Konen O, Schoenfeld T, Straussberg R, Nahum E, Ibrahim AK, Eshel G, Horev G. Thiamine deficiency in infants: MR findings in the brain. *AJNR Am J Neuroradiol*. 2005; 26(7):1668–74. [PubMed: 16091511]
- Korsakoff SS. Psychic disorder in conjunction with multiple neuritis (English translation with commentary). *Neurology*. 1955; 5:394–406. [PubMed: 14383944]
- Krause M, Yang Z, Rao G, Houston FP, Barnes CA. Altered dendritic integration in hippocampal granule cells of spatial learning-impaired aged rats. *J Neurophysiol*. 2008; 99:2769–2778. [PubMed: 18417628]
- Kril JJ. Neuropathology of thiamine deficiency disorders. *Metab Brain Dis*. 1996; 11:9–15. [PubMed: 8815394]
- Kril JJ, Halliday GM, Svoboda MD, Cartwright H. The cerebral cortex is damaged in chronic alcoholics. *Neuroscience*. 1997; 79:983–998. [PubMed: 9219961]
- Krout KE, Belzer RE, Loewy AD. Brainstem projections to midline and intralaminar thalamic nuclei of the rat. *J Comp Neurol*. 2002; 448:53–101. [PubMed: 12012375]
- Langlais PJ. Pathogenesis of diencephalic lesions in an experimental model of Wernicke's encephalopathy. *Metab Brain Dis*. 1995; 10:31–44. [PubMed: 7596327]
- Langlais PJ, Mair RG. Protective effects of the glutamate antagonist MK-801 on pyridoxamine-induced lesions and amino acid changes in rat brain. *J Neurosci*. 1990; 10:1664–1674. [PubMed: 1970604]
- Langlais PJ, Savage LM. Thiamine deficiency in rats produces cognitive and memory deficits on spatial tasks that correlate with tissue loss in diencephalon, cortex and white matter. *Behav Brain Res*. 1995; 68:75–89. [PubMed: 7619308]
- Langlais PJ, Zhang SX. Extracellular glutamate is increased in thalamus during thiamine deficiency-induced lesions and is blocked by MK-801. *J Neurochem*. 1993; 61:2175–2182. [PubMed: 8245970]
- Langlais PJ, Zhang S. Cortical and subcortical white matter damage without Wernicke's encephalopathy after recovery from thiamine deficiency in the rat. *Alcohol Clin Exp Res*. 1997; 68:75–89.
- Langlais PJ, Mandel RJ, Mair RG. Diencephalic lesions, learning impairments, and intact retrograde memory following acute thiamine deficiency in the rat. *Behav Brain Res*. 1992; 48:177–185. [PubMed: 1616608]
- Langlais PJ, Zhang S, Savage LM. Neuropathology of thiamine deficiency: An update on the comparative analysis of human disorders and experimental models. *Metab Brain Dis*. 1996; 11:19–37. [PubMed: 8815388]
- Langlais PJ, Mair RG, Anderson CD, McEntee WJ. Monoamine and metabolites in cortex and subcortical structures: Normal regional distribution and the effects of thiamine deficiency in the rat. *Brain Res*. 1987; 421:140–149. [PubMed: 2446701]
- Langlais PJ, Mair RG, Anderson CD, McEntee WJ. Long-lasting changes during thiamine deficiency-induced lesions and amino acid changes in rat brain. *Neurochem Res*. 1988; 13:1199–1206. [PubMed: 3237312]
- Langlais PJ, McRee RC, Nalwalk JA, Hough LB. Depletion of brain histamine produces regionally selective protection against thiamine deficiency-induced lesions in the rat. *Metab Brain Dis*. 2002; 17:199–209. [PubMed: 12322789]
- Langlais PJ, Zhang SX, Weilerbacher G, Hough LB, Barke KE. Histamine-mediated neuronal death in a rat model of Wernicke's encephalopathy. *J Neurosci Res*. 1994; 38:564–565.

- Lapergue B, Klein I, Olivot JM, Amarenco P. Diffusion weighted imaging of cerebellar lesions in Wernicke's encephalopathy. *J Neuroradiol.* 2006; 33(2):126–128. [PubMed: 16733427]
- LaRoche K, Riche D, Sara SJ. Persistence of habituation deficits after neurological recovery from severe thiamine deprivation. *Brain Res.* 1987; 26:37–46.
- Lee ST, Jung YM, Na DL, Park S, Kim M. Corpus callosum atrophy in Wernicke's encephalopathy. *J Neuroimaging.* 2005; 15:367–372. [PubMed: 16254403]
- Mair RG. On the role of thalamic pathology in diencephalic amnesia. *Rev Neurosci.* 1994; 5:105–140. [PubMed: 7827707]
- Mair RG, Anderson C, Langlais PJ, McEntee WJ. Thiamine deficiency depletes cortical norepinephrine and impairs learning processes in the rat. *Brain Res.* 1985; 360:273–284. [PubMed: 4075172]
- Mair RG, Anderson CD, Langlais PJ, McEntee WJ. Behavioral impairments, brain lesions and monoaminergic activity in the rat following recovery from a bout of thiamine deficiency. *Behav Brain Res.* 1988; 27:223–239. [PubMed: 2896002]
- Mair RG, Knott RL, Rabchenuk SA, Langlais PJ. Impairment of olfactory, auditory, and spatial serial reversal learning in rats recovered from pyriethamine-induced thiamine deficiency. *Behav Neurosci.* 1991; 105:360–374. [PubMed: 1907457]
- Mair RG, McEntee WJ. Cognitive enhancement in Korsakoff's disease by clonidine: A comparison with L-DOPA and ephedrine. *Psychopharmacology.* 1986; 88:374–380. [PubMed: 3083458]
- Mair RG, McEntee WJ, Zatorre RJ. Monoamine activity correlates with psychomimetic deficits in Korsakoff's disease. *Behav Brain Res.* 1985; 15:247–254. [PubMed: 2408635]
- Mair RG, Warrington EK, Weiskrantz L. Memory disorder in Korsakoff's psychosis: A neuropathological and neuropsychological investigation of two cases. *Brain.* 1979; 102:749–783. [PubMed: 116710]
- Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J Neurosci.* 2000; 20(24):9104–10. [PubMed: 11124987]
- Mancinelli R, Ceccanti M, Guiducci MS, Sasso GF, Sebastiani G, Attilia ML, Allen JP. Simultaneous liquid chromatographic assessment of thiamine, thiamine monophosphate and thiamine diphosphate in human erythrocytes: A study on alcoholics. *Journal of Chromatography B.* 2003; 789:355–363.
- Markowitsch HJ. Diencephalic amnesia: A reorientation towards tracts? *Brain Res Rev.* 1988; 13:351–370.
- Matsushita H, Takeuchi Y, Kosaka K, Fushiki S, Kawata M, Sawada T. Changes in serotonergic neurons in the brain of pyriethamine-induced acute thiamine-deficient mice. *Acta Neuropathol.* 1999; 98:614–621. [PubMed: 10603037]
- Mayes AR, Meudell PR, Mann D, Pickering A. Location of lesions in Korsakoff syndrome: Neuropsychological and neuropathological data on two patients. *Cortex.* 1988; 24:367–388. [PubMed: 3191722]
- McEntee WJ, Mair RG. Memory impairment in Korsakoff's psychosis: A correlation with brain noradrenergic activity. *Science.* 1978; 202:905–907. [PubMed: 715450]
- McEntee WJ, Mair RG. Memory enhancement in Korsakoff's psychosis: Further evidence of noradrenergic deficit. *Ann Neurol.* 1980; 27:460–470.
- McRee RC, Terry-Ferguson M, Langlais PJ, Chen Y, Nalwalk JW, Blumenstock FA, Hough LB. Increased histamine release and granulocytes within the thalamus of a rat model of Wernicke's encephalopathy. *Brain Res.* 2000; 858:227–236. [PubMed: 10708674]
- Mitchell AS, Dalrymple-Alford JC. Dissociable memory effects after medial thalamus lesions in the rat. *Eur J Neurosci.* 2005; 22:973–985. [PubMed: 16115220]
- Mitchell AS, Browning PG, Baxter MG. Neurotoxic lesions of the medial mediodorsal nucleus of the thalamus disrupt reinforcer devaluation effects in rhesus monkeys. *J Neurosci.* 2007; 27:11289–11295. [PubMed: 17942723]
- Morris RGM, Garrud P, Rawlins JNP, O'Keefe J. Place navigation impaired in rats with hippocampal lesions. *Nature.* 1982; 297:681–683. [PubMed: 7088155]

- Mousseau DD, Rao V, Butterworth RF. Vesicular dysfunction during experimental thiamine deficiency is indicated by alterations in dopamine metabolism. *Eur J Pharmacol.* 1996; 317:263–267. [PubMed: 8997609]
- Mulholland PJ, Self RL, Stepanyan TD, Littleton HJ, Prendergast MA. Thiamine deficiency in the pathogenesis of chronic ethanol-associated cerebellar damage in vitro. *Neuroscience.* 2005; 135:1129–1139. [PubMed: 16165302]
- Mumby DG, Cameli L, Glenn MJ. Impaired allocentric spatial working memory and intact retrograde memory after thalamic damage caused by thiamine deficiency in rats. *Behav Neurosci.* 1999; 113:42–50. [PubMed: 10197905]
- Mumby DG, Mana MJ, Pinel JP, David E, Banks K. Pyridoxamine-induced thiamine deficiency impairs object recognition in rats. *Behav Neurosci.* 1995; 109(6):1209–14. [PubMed: 8748969]
- Nakagawasai O. Behavioral and neurochemical alterations following thiamine deficiency in rodents: Relationship to functions of cholinergic neurons. *Yakugaku Zasshi.* 2005; 125:549–554. [PubMed: 15997211]
- Nakagawasai O, Murata A, Arai Y, Ohba A, Wakui K, Mitazaki S, Nijima F, Tan-No K, Tadano T. Enhanced head-twitch response to 5-HT-related agonists in thiamine-deficient mice. *J Neural Transm.* 2007; 114:1003–1010. [PubMed: 17372673]
- Nakagawasai O, Tadano T, Hozumi S, Taniguchi R, Tan-No K, Esashi A, Nijima F, Kisara K. Characteristics of depressive behavior induced by feeding thiamine-deficiency diet in mice. *Life Sci.* 2001; 69:1181–1191. [PubMed: 11508350]
- Nakagawasai O, Tadano T, Hozumi S, Tan-No K, Nijima F, Kisara K. Immunohistochemical estimation of brain choline acetyltransferase and somatostatin related to the impairment of avoidance learning induced by thiamine deficiency. *Brain Res Bull.* 2000; 52(3):189–96. [PubMed: 10822160]
- Navarro D, Zwingmann C, Butterworth RF. Region-selective alterations of glucose oxidation and amino acid synthesis in the thiamine-deficient rat brain: Re-evaluation using H/C nuclear magnetic resonance spectroscopy. *J Neurochem.* 2008; 106:603–612. [PubMed: 18410518]
- Neave N, Sahgal A, Aggleton JP. Lack of effect of dorsomedial thalamic lesions on automated tests of spatial memory in the rat. *Behav Brain Res.* 1993; 55:39–49. [PubMed: 8329125]
- Newman LA, Burk JA. Effects of excitotoxic thalamic intralaminar nuclei lesions on attention and working memory. *Behav Brain Res.* 2005; 162:264–271. [PubMed: 15970220]
- Numata S, Hongwei S, Ueno S, Ohmori T. The effect of milnacipran (serotonin noradrenaline reuptake inhibitor) on memory in Korsakoff's syndrome after encephalitis. *Gen Hosp Psychiatry.* 2005; 27:224–226. [PubMed: 15882773]
- Oler JA, Markus EJ. Age-related deficits in the ability to encode contextual change: A place cell analysis. *Hippocampus.* 2000; 10(3):338–50. [PubMed: 10902903]
- Onodera K, Ogura Y, Kisara K. Characteristics of muricide induced by thiamine deficiency and its suppression by antidepressants or intraventricular serotonin. *Physiol Behav.* 1981; 27:847–53. [PubMed: 7198802]
- Onodera K, Saito T, Itoh M. Changes in blood pressure and heart rate following dietary-induced thiamine deficiency in muricide rats. *Jpn J Psychopharm.* 1991; 11:319–325.
- Paller KA, Acharya A, Richardson BC, Plaisent O, Shimamura AP, Reed BR, Jagust WJ. Functional neuroimaging of cortical dysfunction in alcoholic Korsakoff's syndrome. *J Cogn Neurosci.* 1997; 9:277–293.
- Park LC, Zhang H, Sheu KF, Calingasan NY, Kristal BS, Lindsay JG, Gibson GE. Metabolic impairment induces oxidative stress, compromises inflammatory responses, and inactivates a key mitochondrial enzyme in microglia. *J Neurochem.* 1999; 72:1948–1958. [PubMed: 10217272]
- Parkin AJ, Blunden J, Rees JE, Hunkin NM. Wernicke-Korsakoff syndrome of nonalcoholic origin. *Brain Cogn.* 1991; 15(1):69–82. [PubMed: 1901211]
- Parkin AJ, Dunn JC, Lee C, O'Hara PF, Nussbaum L. Neuropsychological sequelae of Wernicke's encephalopathy in a 20-year-old woman: selective impairment of a frontal memory system. *Brain Cogn.* 1993; 21(1):1–19. [PubMed: 8424858]

- Pekovich SR, Martin PR, Singleton CK. Thiamine deficiency decreases steady-state transketolase and pyruvate dehydrogenase but not α -ketoglutarate dehydrogenase mRNA levels in three human cell types. *J Nutr.* 1998; 128:683–687. [PubMed: 9521628]
- Pfefferbaum A, Adalsteinsson E, Bell RL, Sullivan EV. Development and resolution of brain lesions caused by pyriethamine- and dietary-induced thiamine deficiency and alcohol exposure in the alcohol-preferring rat: A longitudinal magnetic resonance imaging and spectroscopy study. *Neuropsychopharmacology.* 2007; 32:1159–1177. [PubMed: 16723995]
- Pires RG, Perira S, Oliveira-Silva IF, Franco GC, Ribeiro AM. Cholinergic parameters and the retrieval of learned and re-learned spatial information: A study using a model of Wernicke-Korsakoff syndrome. *Behav Brain Res.* 2005; 162:11–21. [PubMed: 15922063]
- Pires RG, Perira S, Pittella J, Franco GC, Ferreira C, Fernandes PA, Ribeiro AM. The contribution of mild thiamine deficiency and ethanol consumption to central cholinergic parameter dysfunction and rats' open-field performance impairment. *Pharmacol Biochem Behav.* 2001; 70:227–235. [PubMed: 11701192]
- Pitkin SR, Savage LM. Aging potentiates the acute and chronic neurological symptoms of pyriethamine-induced thiamine deficiency in the rodent. *Behav Brain Res.* 2001; 119:167–177. [PubMed: 11165332]
- Pitkin SR, Savage LM. Age-related vulnerability to diencephalic amnesia produced by thiamine deficiency: The role of time of insult. *Behav Brain Res.* 2004; 148:93–105. [PubMed: 14684251]
- Reed LJ, Lasserson D, Marsden P, Stanhope N, Stevens T, Bello F, Kingsley D, Colchester A, Kopelman MD. FDG-PET findings in Wernicke-Korsakoff syndrome. *Cortex.* 2003; 39:1027–1045. [PubMed: 14584565]
- Robinson JK, Mair RG. MK-801 prevents brain lesions and delayed-nonmatching-to-sample deficits produced by pyriethamine-induced encephalopathy in rats. *Behav Neurosci.* 1992; 106:623–33. [PubMed: 1386989]
- Roland JJ, Savage LM. Hippocampal and striatal acetylcholine efflux during learning in diencephalic-lesioned rats. *Neurobio Learn Mem.* 2007; 87:123–132.
- Roland JJ, Savage LM. Blocking GABA-A receptors in the medial septum enhances hippocampal acetylcholine release and behavior in a rat model of diencephalic amnesia. *Pharmacol Biochem Behav.* 2009a; 92:480–487.
- Roland JJ, Savage LM. The role of cholinergic and GABAergic medial septal/diagonal band cell populations in the emergence of diencephalic amnesia. *Neuroscience.* 2009b; 160:32–41. [PubMed: 19264109]
- Roland J, Mark K, Vetreno RP, Savage LM. Increasing hippocampal acetylcholine enhance behavioral performance in an animal model of diencephalic amnesia. *Brain Res.* 2008; 1234:116–127. [PubMed: 18706897]
- Saad L, Silva LF, Banzato CE, Dantas CR, Garcia C Jr. Anorexia nervosa and Wernicke-Korsakoff syndrome: a case report. *J Med Case Reports.* 2010; 4:217. [PubMed: 20646296]
- Savage LM, Castillo R, Langlais PJ. Effects of lesions of thalamic intralaminar and midline nuclei and internal medullary lamina on spatial memory and object discrimination. *Behav Neurosci.* 1998; 112:1339–1352. [PubMed: 9926817]
- Savage LM, Chang Q, Gold PE. Diencephalic damage decreases hippocampal acetylcholine release during spontaneous alternation testing. *Learn Mem.* 2003; 10:242–246. [PubMed: 12888541]
- Savage LM, Pitkin SR, Knitowski KM. Rats exposed to acute pyriethamine-induced thiamine deficiency are more sensitive to the amnesic effects of scopolamine and MK-801: Examination of working memory, response selection, and reinforcement contingencies. *Behav Brain Res.* 1999; 104:13–26. [PubMed: 11125732]
- Savage LM, Ramos RL. Reward expectation alters learning and memory: the impact of the amygdala on appetitive-driven behaviors. *Behav Brain Res.* 2009; 198(1):1–12. [PubMed: 19022299]
- Savage LM, Roland JJ, Klintsova AY. Selective septohippocampal-but not forebrain amygdalar-cholinergic dysfunction in diencephalic amnesia. *Brain Res.* 2007; 1139:210–219. [PubMed: 17289001]
- Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. *Lancet Neurol.* 2007; 6(5):442–55. [PubMed: 17434099]

- Schiff ND. Central thalamic contributions to arousal regulation and neurological disorders of consciousness. *Ann N Y Acad Sci.* 2008; 1129:105–118. [PubMed: 18591473]
- Shelton MK, McCarthy KD. Hippocampal astrocytes exhibit Ca²⁺-elevating muscarinic, cholinergic and histaminergic receptors in situ. *J Neurochem.* 2000; 74:555–563. [PubMed: 10646506]
- Shen J, Barnes CA, McNaughton BL, Skaggs WE, Weaver KL. The effect of aging on experience-dependent plasticity of hippocampal place cells. *J Neurosci.* 1997; 17:6769–6782. [PubMed: 9254688]
- Sheu KF, Calingasan NY, Lindsay JG, Gibson GE. Immunochemical characterization of the deficiency of the α -ketoglutarate dehydrogenase complex in thiamine-deficient rat brain. *J Neurochem.* 1998; 70:1143–1150. [PubMed: 9489735]
- Squire LR, Zola-Morgan S, Chen KS. Human amnesia and animal models of amnesia: performance of amnesic patients on tests designed for the monkey. *Behav Neurosci.* 1988; 102(2):210–21. [PubMed: 3130073]
- Steinbusch, HM.; Verhofstad, AJ. Immunocytochemical demonstration of noradrenaline, serotonin and histamine and some observations of the innervations of the intracerebral blood vessels. In: Owman, C.; Hardebo, JE., editors. *Neural regulation of brain circulation.* Holland: Elsevier; 1986. p. 181–194.
- Sugai A, Kikugawa K. Atypical MRI findings of Wernicke encephalopathy in alcoholic patients. *AJR Am J Roentgenol.* 2010; 195(5):W372–3. [PubMed: 20966303]
- Sullivan EV, Pfefferbaum A. Neuroimaging of the Wernicke-Korsakoff syndrome. *Alcohol Alcohol.* 2009; 44(2):155–65. [PubMed: 19066199]
- Sullivan EV, Deshmukh A, Desmond JE, Lim KO, Pfefferbaum A. Cerebellar volume decline in normal aging, alcoholism, and Korsakoff's syndrome: Relation to ataxia. *Neuropsychology.* 2000; 14:341–352. [PubMed: 10928737]
- Sutherland RJ, Sparks FT, Lehmann H. Hippocampus and retrograde amnesia in the rat model: A modest proposal for the situation of systems consolidation. *Neuropsychologia.* 2010; 48:2357–2369. [PubMed: 20430043]
- Takahashi H, Nakazawa S, Yoshino Y, Shimura T. Metabolic studies of the edematous cerebral cortex of the pyridoxamine-treated thiamine-deficient rat. *Brain Res.* 1988; 441(1–2):202–8. [PubMed: 3359230]
- Taube JS, Bassett JP. Persistent neural activity in head direction cells. *Cereb Cortex.* 2003; 13:1162–1172. [PubMed: 14576208]
- Thompson SG, McGeer EG. GABA-transaminase and glutamic acid decarboxylase changes in the brain of rats treated with pyridoxamine. *Neurochem Res.* 1985; 10:1653–1660. [PubMed: 4088435]
- Thomson AD, Cook CCH, Guerrini I, Sheedy D, Harper C, Marshall EJ. Wernicke's encephalopathy revisited: Translation of the case history section of the original manuscript by Carl Wernicke 'Lehrbuch der Gehirnkrankheiten für Aerzte und Studierende' (1881) with a commentary. *Alcohol Alcohol.* 2008; 43:174–179. [PubMed: 18056751]
- Thomson AD, Cook CCH. Parenteral thiamine and Wernicke's encephalopathy: The balance of risks and perception of concern. *Alcohol and Alcoholism.* 1997; 32:207–209. [PubMed: 9199720]
- Thomson AD, Cook CCH, Touquet R, Henry JA. The Royal College of Physicians report on alcohol: guidelines for managing Wernicke's encephalopathy in the Accident and Emergency Department. *Alcohol and Alcoholism.* 2002; 37:513–521. [PubMed: 12414541]
- Todd KG, Butterworth RF. Evaluation of the role of NMDA-mediated excitotoxicity in the selective neuronal loss in experimental Wernicke's encephalopathy. *Exp Neurol.* 1998; 149:130–138. [PubMed: 9454622]
- Todd KG, Butterworth RF. Early microglial response in experimental thiamine deficiency: An immunohistochemical analysis. *Glia.* 1999; 25:190–198. [PubMed: 9890633]
- Todd KG, Butterworth RF. Mechanisms of selective neuronal cell death due to thiamine deficiency. *Annals of the New York Academy of Sciences.* 1999; 893:404–411. [PubMed: 10672278]
- Tomasi D, Chang L, Caparelli EC, Ernst T. Different activation patterns for working memory load and visual attention load. *Brain Res.* 2007; 1132:158–165. [PubMed: 17169343]

- Troncoso JC, Johnston MV, Hess KM, Griffin JW, Price DL. Model of Wernicke's encephalopathy. *Arch Neurol*. 1981; 38:350–354. [PubMed: 7236062]
- Trotti D, Danbolt NC, Volterra A. Glutamate transporters are oxidant-vulnerable: A molecular link between oxidative and excitotoxic neurodegeneration? *Trends Pharmacol Sci*. 1998; 19:328–334. [PubMed: 9745361]
- Trotti D, Rossi D, Gjesdal O. Peroxynitrite inhibits glutamate transporter subtypes. *J Biol Chem*. 1996; 271:5976–5979. [PubMed: 8626378]
- Van der Werf YD, Witter MP, Groenewegen HJ. The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. *Brain Res Rev*. 2002; 39:107–140. [PubMed: 12423763]
- Van der Werf YD, Witter MP, Uylings HB, Jolles J. Neuropsychology of infarctions in the thalamus: A review. *Neuropsychologia*. 2000; 38:613–627. [PubMed: 10689038]
- Van Groen T, Wyss JM. Projections from the anterodorsal and anteroventral nucleus of the thalamus to the limbic cortex in the rat. *J Comp Neurol*. 1995; 358:584–604. [PubMed: 7593752]
- van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci*. 1999; 2(3):266–70. [PubMed: 10195220]
- Van Woert MH, Plaitakis A, Hwang EC, Berl S. Effect of thiamine deficiency on brain serotonin turnover. *Brain Res*. 1979; 179:103–110. [PubMed: 509224]
- Vertes RP, Albo Z, Di Prisco GV. Theta-rhythmically firing neurons in the anterior thalamus: Implications for mnemonic functions of Papez's circuit. *Neuroscience*. 2001; 104:619–625. [PubMed: 11440795]
- Vetreno RP, Anzalone SJ, Savage LM. Impaired, spared and enhanced ACh efflux across the hippocampus and striatum in diencephalic amnesia is dependent on task demands. *Neurobiol Learn Mem*. 2008; 90:237–244. [PubMed: 18472286]
- Vetreno RP, Klintsova A, Savage LM. Stage-dependent alterations of progenitor cell proliferation and neurogenesis in an animal model of Wernicke-Korsakoff syndrome. *Brain Res*. 2011; 19(1391): 132–46. [PubMed: 21440532]
- Victor, M.; Adams, RD.; Collins, GH. The Wernicke-Korsakoff syndrome and related neurologic disorders due to alcoholism and malnutrition. Philadelphia: F.A. Davis; 1989.
- Vigil F, Oliveira-Silva I, Ferreira LF, Pereira S, Ribeiro AM. Spatial memory deficits and serotonergic metabolite change in thiamine deficient rats. *Beh Brain Res*. 2010; 210:140–142.
- Volterra A, Trotti D, Tromba C. Glutamate uptake inhibition of oxygen free radicals in rat cortical astrocytes. *J Neurosci*. 1994; 14:2924–2932. [PubMed: 7910203]
- Warburton EC, Aggleton JP. Differential deficits in the Morris water maze following cytotoxic lesions of the anterior thalamus and fornix transection. *Behav Brain Res*. 1999; 98:27–38. [PubMed: 10210519]
- Warburton EC, Baird AL, Morgan A, Muir JL, Aggleton JP. Disconnecting hippocampal projections to the anterior thalamus produces deficits on tests of spatial memory in rats. *Eur J Neurosci*. 2000; 12:1714–1726. [PubMed: 10792449]
- Watanabe I, Kanabe S. Early edematous lesion of pyridoxamine induced acute thiamine deficient encephalopathy in the mouse. *J Neuropathol Exp Neurol*. 1978; 37(4):401–13. [PubMed: 681983]
- Witt ED, Goldman-Rakic PS. Intermittent thiamine deficiency in the rhesus monkey. II Evidence for memory loss. *Ann Neurol*. 1983; 13(4):396–401. [PubMed: 6404215]
- Yang G, Gong YD, Gong K, Jiang WL, Kwon E, Wang P, Zheng H, Zhang XF, Gan WB, Zhao NM. Reduced synaptic vesicle density and active zone size in mice lacking amyloid precursor protein (APP) and APP-like protein 2. *Neurosci Lett*. 2005; 384:66–71. [PubMed: 15919150]
- Yu C, Gupta J, Yin HH. The role of mediodorsal thalamus in temporal differentiation of reward-guided actions. *Front Integr Neurosci*. 2010; 21:14. 4.pii.
- Zhang SX, Weilersbacher GS, Henderson SW, Corso T, Olney JW, Langlais PJ. Excitotoxic cytopathology, progression, and reversibility of thiamine deficiency-induced diencephalic lesions. *J Neuropathol Exp Neurol*. 1995; 54:255–267. [PubMed: 7876893]

- Zhao N, Zhong C, Wang Y, Zhao Y, Gong N, Zhou G, Xu T, Hong Z. Impaired hippocampal neurogenesis is involved in cognitive dysfunction induced by thiamine deficiency at early pre-pathological lesion stage. *Neurobiol Dis.* 2008; 29:176–185. [PubMed: 17936635]
- Zuccoli G, Pipitone N. Neuroimaging findings in acute Wernicke's encephalopathy: review of the literature. *AJR Am J Roentgenol.* 2009 Feb; 192(2):501–8. [PubMed: 19155417]
- Zuccoli G, Santa Cruz D, Bertolini M, Rovira A, Gallucci M, Carollo C, Pipitone N. MR imaging findings in 56 patients with Wernicke encephalopathy: Nonalcoholics may differ from alcoholics. *Am J Neuroradiol.* 2009; 30:171–176. [PubMed: 18945789]
- Zuccoli G, Siddiqui N, Cravo I, Bailey A, Gallucci M, Harper CG. Neuroimaging findings in alcohol-related encephalopathies. *AJR Am J Roentgenol.* 2010b; 195(6):1378–84. [PubMed: 21098198]
- Zuccoli G, Siddiqui N, Bailey A, Bartoletti SC. Neuroimaging findings in pediatric Wernicke encephalopathy: a review. *Neuroradiology.* 2010c; 52:523–39. [PubMed: 19844698]

Figure 1.

Neurodegeneration of thalamic nuclei after PTD treatment. Coronal sections of the thalamus and staining of NeuN immunoreactive neurons in the thalamus of Control (A, C) and PTD-treated rats (B, D). Rostral (A, B) and more caudal (C, D) levels of the thalamus are shown for comparison. Abbreviations; AD: Anterodorsal nucleus, ADDM: Anteroventral thalamic nucleus/dorsomedial division; ADVM: Anteroventral thalamic nucleus/ventrolateral division; 3V: third ventricle; D3V: Dorsal third ventricle stria medullaris; PC: Paracentral thalamic nucleus; CM: Central median nucleus; CM: Central lateral nucleus.

Table 1

Comparison of the behavioral presentation of TD in humans and in rodent models of TD

Behavioral Symptoms:	Clinical Presentation in Humans:	Rodent Model of ID:
Anorexia	<i>NO</i>	+
Apnea	+	<i>NT</i>
Ataxia	+	+
Bradycardia	+	<i>tachycardia</i>
Depressive symptoms	<i>NO</i>	+
Dysarthria	+	<i>NO</i>
Hearing loss	+	<i>NT</i>
Hypotension	+	<i>NO</i>
Loss of consciousness	+	+
Mental status change	+	+
Motor incoordination	+	+
Nystagmus	+	+
Oculomotor dysfunction	+	<i>NT</i>
Opisthotonus	<i>NO</i>	+
Postural dysfunction	+	+
Seizure	+	+
Startle response	<i>NT</i>	+
Anterograde memory loss	+	+
Retrograde memory loss	+	<i>NO</i>

NO: Not observed

NT: Not tested

Table 2

Comparison of neuroimaging and neuropathology findings in humans with TD and in rodent models of TD

Brain Structure	Neuroimaging Findings in Humans	Rodent Neuropathology	Rodent Neuroimaging
Cerebellum	Atypical	+	+
Corpus callosum	Atypical	+	+
Cranial nerve nuclei	Atypical	+	<i>NO</i>
Frontal cortex	Atypical	+	+
Mammillary bodies	Typical	+	+
Medulla	Atypical	+	<i>NO</i>
Parietal cortex	Atypical	+	<i>NO</i>
Periaqueductal gray	Typical	+	+
Red Nucleus	Atypical	<i>NO</i>	<i>NO</i>
Striatum	Atypical	<i>NO</i>	<i>NO</i>
Tectum	Typical	+	+
Thalamus	Typical	+	+

NO: Not observed