

Brief Communication

Diencephalic Damage Decreases Hippocampal Acetylcholine Release During Spontaneous Alternation Testing

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A rodent model of diencephalic amnesia, pyriethamine-induced thiamine deficiency (PTD), was used to investigate diencephalic-hippocampal interactions. Acetylcholine (ACh) release, a marker of memory-related activation, was measured in the hippocampus of PTD-treated and control rats prior to, during, and after spontaneous alternation test. During behavioral testing, all animals displayed increases in ACh release. However, both the percent increase of ACh release during spontaneous alternation testing and the alternation scores were higher in control rats relative to PTD-treated rats. Thus, when rats are tested on a task with demands dependent on the hippocampus, it appears that the hippocampus is not fully activated after diencephalic damage.

Diencephalic lesions can cause severe and long-lasting amnesia. Damage to certain nuclei and fiber systems within the diencephalon interrupt the flow of information between key memory structures. Specifically, the diencephalon may serve as a link between limbic and cortical structures, and damage to the diencephalon can contribute to amnesia through what has been called a “disconnection syndrome” (Warrington and Weiskrantz 1982; Markowitsch 1988; Aggleton and Brown 1999). Evidence from animal lesion studies and human patients points toward the following diencephalic structures in the production of amnesia: medial dorsal thalamic nucleus, anterior thalamic nuclei, mammillary bodies, and the internal medullary lamina (Mair 1994; Langlais et al. 1996; Aggleton and Pearce 2001). Although there is evidence that lesions to particular diencephalic nuclei result in memory impairment in their own right (Mair 1994), there is also evidence that damage to diencephalic nuclei can disrupt memory circuits leading to dysfunction in other regions of the brain (Warrington and Weiskrantz 1982; Markowitsch 1988).

A prominent model of diencephalic amnesia is pyriethamine-induced thiamine deficiency (PTD). This dietary manipulation is used to model the human disorder of Wernicke-Korsakoff Syndrome (WKS), a nutritional disorder associated with chronic alcoholism (Kopelman 1995). Although diencephalic pathology was clearly established in WKS patients (Victor and Adams 1971), this patient population was pivotal in the development of the theoretical dual memory dissociation between declarative (hippocampal-based memory) and nondeclarative (nonhippocampal memory) memory processes (Squire 1982). This is somewhat perplexing given that it was clear from post-mortem and neuroimaging studies that the most consistent neuropathology of WKS is damage to the diencephalon—particularly the thalamus and mammillary bodies; few WKS patients had hippocampal pathology (Kopelman 1995). In addition, the PTD model has provided support for the claim that the diencephalic damage is critical to the learning and memory impairments as-

sociated with thiamine deficiency (Mair et al. 1988; Mair 1994; Aggleton and Pearce 2001).

Reviews of the pathology produced by the PTD treatment have consistently demonstrated that although mild to moderate cell loss occurs outside the diencephalon, the anterior and midline thalamic damage are critical and responsible for the majority of the loss of learning and memory function that occurs after thiamine deficiency (Mair 1994; Langlais et al. 1996). However, the PTD model not only results in acute neurological disturbances and diencephalic lesions; there are also chronic adaptations in numerous neurotransmitter systems (norepinephrine, serotonin, glutamate and acetylcholine) in regions outside of the diencephalon (Mair et al. 1988; Langlais and Zhang 1997; Pitkin and Savage 2001). These changes, along with the white matter loss that occurs in key fiber tracts from the diencephalon after PTD treatment (Langlais and Zhang 1997) suggest that thiamine deficiency likely causes system-level dysfunction. There is neurobiological evidence that even discrete diencephalic damage alters the activation of other limbic regions, in particular, the hippocampus (Jenkins et al. 2002). Thus, damage to the diencephalon produced by thiamine deficiency likely produces dysfunction in other limbic regions. Our initial attempts to examine this issue failed to find changes in hippocampal acetylcholine (ACh) levels in PTD-treated rats, relative to control pair-fed rats, using a radiometric assay of post mortem tissue (Langlais et al. 1996). One reason for our lack of a PTD-induced effect on hippocampal ACh levels may be because of the fact that the neurochemical procedures used do not allow for temporal monitoring of neurotransmitter levels as a function of behavior. Neurotransmitter dysfunction may not be evident after diencephalic damage until the system is engaged by behavioral demands.

In the current experiment, we examined whether thiamine deficiency, which causes diencephalic pathology, alters hippocampal ACh release when rats are actively exploring a maze. Measurement of ACh release in the brains of rats during learning appears to be a useful marker of activation of a given neural system—particularly the hippocampus (Fadda et al. 1996, 2000; Ragozzino et al. 1996; McIntyre et al. 2002). We chose a task, spontaneous alternation, which is sensitive to diencephalic damage (Langlais and Savage 1995) and to changes in release of ACh in the hippocampus (Ragozzino et al. 1996; McIntyre et al. 2002).

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Twelve young male Sprague-Dawley rats (3–4 months; 250–300 g) were used as subjects in this study. They were housed one per cage with unlimited access to water and Purina rodent chow in a colony room with a 12-hour/12-hour light-dark cycle (onset at 7:00 am).

Animals were first randomly assigned to one of the following treatments: (1) pair-fed control (PF, $n = 6$), or (2) PTD ($n = 6$) groups. Subjects in the PTD group were free-fed a thiamine-deficient chow (Teklad Diets) and given daily injections (0.25 mg/kg, i.p.) of pyrithiamine hydrobromide (Sigma). On days 14–16 of treatment, animals display signs of local tonic movement of the front and hind limbs, and generalized convulsions (seizures). Within 4 h after observing the onset of seizure, PTD-treated animals were given an injection of thiamine (100 mg/kg, i.p.) every 8 h until the seizure activity disappeared and animals regained upright posture. The PF animals were fed an amount of thiamine-deficient chow equivalent to the average amount consumed by the PTD groups on the previous day of treatment and were given daily injections of thiamine (0.4 mg/kg i.p.). After treatment, all subjects were placed on regular chow and allowed to regain the weight lost during treatment.

Three weeks after recovering from PTD or PF treatments, stereotaxic surgery (David Kopf Instruments, USA) was performed on animals anesthetized with sodium pentobarbital (50 mg/kg, i.p.). A plastic guide cannula (CMA/12, Carnegie Medicine Associates) was lowered into the left hippocampus at coordinates 4.7 mm posterior to bregma, 5.0 mm lateral to the midline, and 3.8 mm ventral from dura, according to the atlas of Paxinos and Watson (1986). Two days after surgery, animals were handled daily (5 min/day) for 5 d prior to behavioral testing.

One week following surgery a 3-mm microdialysis probe (CMA/12) was inserted through the guide cannula. The probe was connected to plastic tubing and driven by a microinfusion system (CMA/100). The dialysis probe was perfused continuously at a rate of 2.0 μ L/min with artificial CSF (in mM: 128 NaCl, 2.5 KCL, 1.3 CaCl₂, 2.1 MgCl₂, NaH₂PO₄, 1.3 NaHPO₄, and 1.0 glucose, brought to a pH of 7.4), which contained the acetylcholinesterase inhibitor neostigmine (100 nM). Prior to maze testing, the microdialysis probe was inserted into the hippocampal cannula, and the animal was placed into the holding cage (41 cm \times 30 cm \times 35 cm) located in the testing room. After 60 min of stabilization, dialysis samples (sample volume 16 μ L) were collected every 8 min for a period of 40 min in the holding cage to determine basal levels of ACh in awake rats. During this initial baseline phase, the animal was free to move about the holding

cage. After initial exploration, most animals sat in a corner and occasionally groomed. After five baseline samples were collected, the rat was gently picked up and placed on the center of the maze. The plus-maze was made of wood with clear Plexiglas side-walls (12-cm high) and a painted black floor with the four arms of equal distance (55 cm) was used for training. It was elevated 80 cm from the floor. The rat was allowed to transverse the maze freely for 40 min. The number and sequence of arms entered were recorded to determine alternation scores (Ragozzino et al. 1996; McIntyre et al. 2002).

An alternation was defined as the choice of an arm to the left or right of the rat when it reached the center area, not the arm straight ahead or a reenter into the same arm. The percent alteration score is equal to the ratio of: (actual alternations/possible alteration) \times 100. The maze testing room contained various extramaze cues (posters, doors, tables, etc). Upon completion of 40 min of maze testing, rats were transferred back to the holding cage, and postbaseline levels of ACh were collected for an additional 40 min. Similar to the prebaseline period, during the post-baseline period, the animal was free to move about the holding cage.

Dialysate samples were assayed for ACh using HPLC with electrochemical detection (Bio Analytic Systems). The system included an ion-exchange microbore analytical column, a microbore ACh/Ch immobilized enzyme reactor containing acetylcholinesterase and choline oxidase, and a peroxidase wired working electrode. The detection limit of this system is 5 fmol. ACh peaks were quantified by comparison to peak heights of standard solutions and corrected for in-vitro recovery of the probe.

At the end of the experiment, rats were given a lethal dose of sodium pentobarbital, and their brains were removed and coronal sections cut and stained with cresyl violet. Probe location and diencephalic lesion status were determined.

The probes of all subjects were located entirely within in the hippocampal formation (Fig. 1). However, one PTD subject's probe came off prior to testing. This animal was not behaviorally tested. Two of the remaining five PTD animals had extensive lesions of the diencephalon (Fig. 1), whereas the remaining three showed some diencephalic tissue loss. Intraventricular distance (IVD; the distance between the roof and floor of the third ventricle) at the midline thalamus (Interaural = 5.86 mm, according to Paxinos and Watson, [1986]) was recorded to document thalamic tissue loss (Langlais and Savage 1995; Pitkin and Savage 2001). PTD-treated rats (mean = 2.37 mm; S.E. = 0.09 mm) had a significantly reduced IVD relative to PF subjects (2.61 mm + 0.03

A. PTD induced lesion

B. PF control

C. Probe location

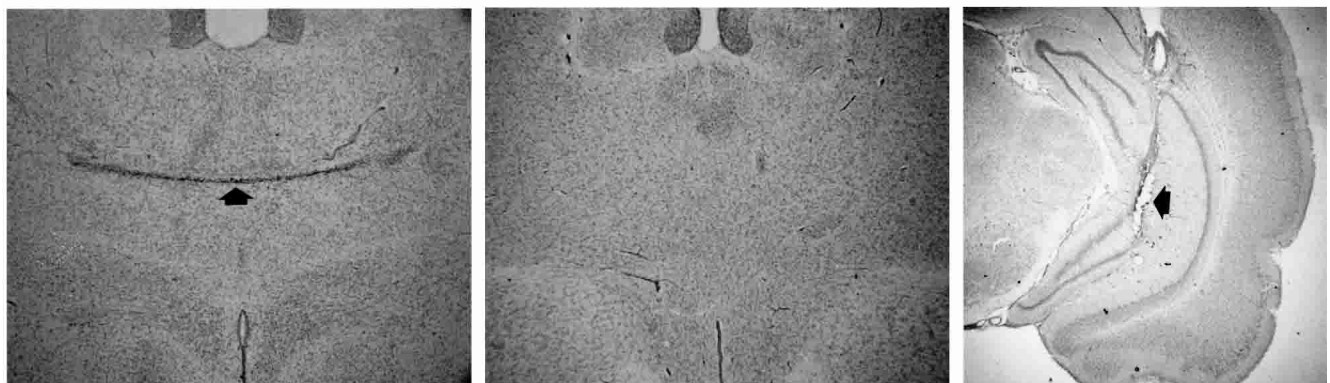


Figure 1 Photomicrographs illustrating a midline thalamic lesion produced by PTD treatment (A), relative to a PF control (B). The last photomicrograph (C) is representative of the hippocampal probe placement.

mm), which did not display any diencephalic damage ($F[1, 9] = 5.68, P < .05$). The diencephalic tissue loss across PTD studies is remarkably similar and this study is no exception. PTD treated rats with this degree of thalamic loss (10% reduction in IVD) have a loss of neurons (40%) in the anterior thalamus (Langlais and Savage 1995) and loss of cells (22%) staining positive for choline acetyltransferase (ChAT-) in the septal area (Pitkin and Savage, 2001).

As shown in Figure 2, PTD-treated rats, relative to PF rats, had a significantly lower level of alternation behavior ($F[1, 9] = 9.25, P < .02$). However, the groups did not differ in the number of arms entered during the testing session ($F[1, 9] < 1$). Hippocampal ACh levels increased during behavioral testing ($F[2, 18] = 16.78, P < .01$; Fig. 3A). However, Figure 3B shows that PTD-treated rats had a significantly lower level of hippocampal ACh release (expressed as percent increase above baseline values) during behavioral testing, relative to PF rats ($F[1, 9] = 7.04, P < .03$). For the regression analysis (Fig. 3C), alternation scores were correlated with mean percent increases of ACh during testing. A positive correlation ($r = 0.603, P < .05$) was found between percent alternation and percent increase of hippocampal ACh during testing (expressed as percent with respect to baseline values).

Our data support previous studies demonstrating that diencephalic-lesioned rats have impaired spontaneous alternation performance (Langlais and Savage 1995). The present findings suggest that this behavioral impairment produced by diencephalic damage is accompanied by decreased release of ACh in the hippocampus during behavioral testing. Of particular interest is the finding that the cholinergic deficit in PTD-treated rats is only evident when the environmental conditions require hippocampal processing: Diencephalic-lesioned rats only display a reduction in hippocampal ACh release during spontaneous alternation testing—not during pre- or postbaseline conditions. The positive correlation between the relative rise in ACh hippocampal levels and spontaneous alternation performance suggest that altered levels of ACh in the hippocampus play at least a modulatory role in some of the impaired cognitive abilities seen in diencephalic-lesioned rats.

Although the role of the septo-hippocampal cholinergic system in spatial memory has been questioned by findings demonstrating that the use of the cholinergic immunotoxin 192-IgG saporin does not impair some forms of spatial learning and memory (Berger-Sweeney et al, 1994; Baxter et al, 1995), the issue of residual and compensatory changes in the cholinergic system after damage has not been widely addressed (Gutierrez et al. 1999; Sarter and Bruno 1997). A number of compensatory changes in the hippocampus occurs after administration of 192-IgG-saporin (see Harrell et al. 2001; Pokala et al. 2002). Further-

more, rats with 192-IgG-saporin lesions of the basal forebrain display decreased rates of alternation behavior (Johnson et al. 2002; Chang and Gold 2003). In addition, relative to sham-operated rats, rats with 192 IgG saporin lesions have decreased hippocampal ACh release at baseline but, still display a rise in hippocampus ACh release during behavioral testing (Chang and Gold 2003). The revised role of the forebrain cholinergic system in learning and memory is more global than originally proposed: ACh regulates a number of cognitive/behavioral processes such as, arousal, attention, temporal processing—all of which are important to learning and memory functioning. ACh appears to have a modulatory rather than central role in the production of behavior related to learning and memory processing (Sarter and Bruno 1997; Gold 2002).

Nonetheless, the measurement of ACh release in the brains of rats during learning and memory processing appears to be a useful marker of activation of a given neural system (Fadda et al. 1996, 2000; Ragozzino et al. 1996; McIntyre et al. 2002). However, under different environmental and behavioral conditions, the magnitude of ACh release varies between and within different brain structures (Gold 2002; McIntyre et al. 2002). Similar to the dissociative lesion studies, microdialysis assessment of ACh in behaving animals reveals region-specific task dependency (McIntyre et al. 2002). Thus, measurements of ACh release offer an innovative way to assess the interactions between memory structures during various environmental conditions during behavioral testing.

High levels of spontaneous alternation are consistent with good spatial memory performance (Langlais and Savage 1995). Although spontaneous alternation has been labeled a hippocampal-dependent task (Isaacson 2002; McIntyre et al. 2002, 2003), lesions of a number of limbic and nonlimbic structures decrease spontaneous alternation rates (for review, see Lalonde 2002). The role of acetylcholine in spontaneous alternation has been examined using drugs that modulate ACh levels, with the majority of findings indicating that increasing ACh levels increases alternation rates and decreasing ACh levels decreases alternation rates; however, there is also evidence of an inverted U curve with high levels of ACh (Lalonde 2002). In addition, hippocampal levels of ACh rise when animals are performing a spontaneous alternation tasks (Ragozzino et al. 1996; Stefani and Gold 2001).

Although hippocampal damage has not been reported in the PTD model (Mair 1994; Langlais et al. 1996), the hippocampal dysfunction we report after diencephalic damage produced by PTD treatment is likely related to two factors: (1) damage to key nuclei and fiber tracts that are integral parts of the extended limbic system after PTD treatment (Langlais and Zhang 1997), and (2) a decrease in the number of cholinergic neurons of the basal forebrain, which send projections to the hippocampus, in PTD-treated rats (Pitkin and Savage 2001). After PTD treatment, there is extensive neuronal loss in the anterior, midline thalamus, and mammillary bodies (Mair et al. 1988; Mair 1994; Langlais and Savage 1995; Langlais et al. 1996). There is also degeneration in the mamillo-thalamic tract and fornix, as well as in the axons projecting to the frontal cortex (Langlais and Zhang 1993, 1997). The damage to both key thalamic nuclei and fiber tracts likely results in a “disconnection syndrome” (Warrington and Weiskrantz 1982; Markowitsch 1988; Aggleton and Brown 1999).

The current study, using such microdialysis techniques, provides evidence that

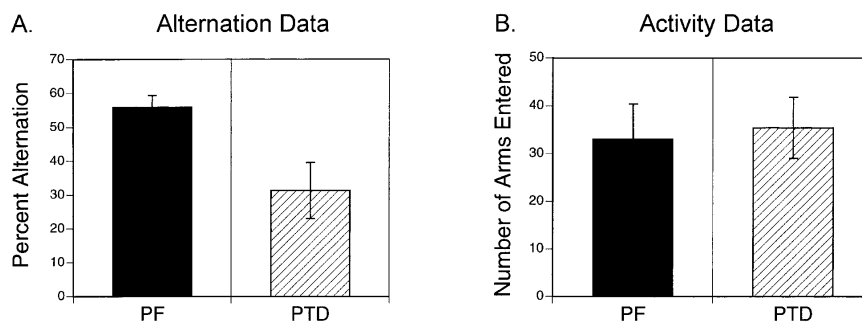


Figure 2 Behavioral data (Mean \pm SEM) from a single session of spontaneous alternation testing for diencephalic-lesioned (PTD) and control (PF) rats. Panel A shows that significant difference between PTD and PF rats in alternation behavior. Panel B shows that groups did not differ in the number of arms transversed during the session.

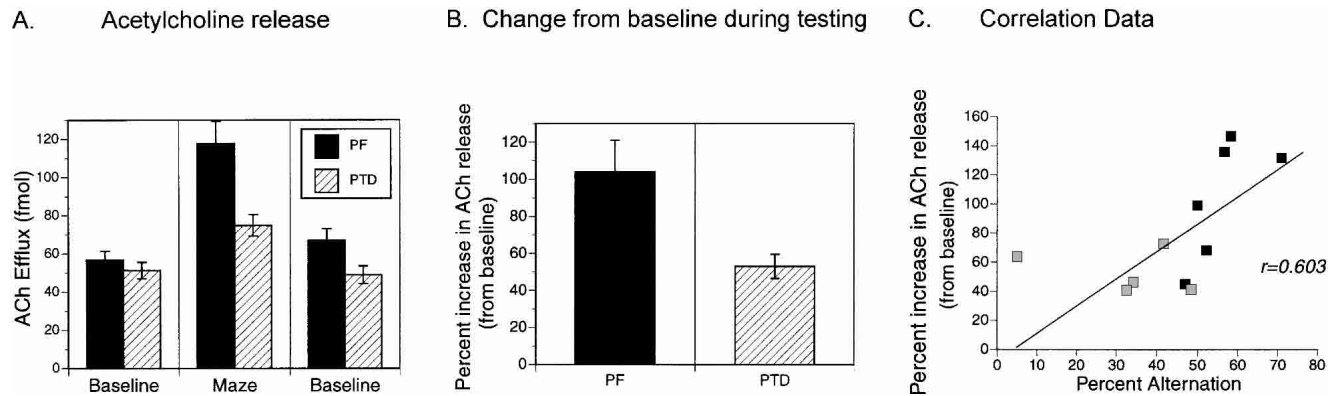


Figure 3 Changes in hippocampal ACh levels as a function of behavioral testing in diencephalic-lesioned (PTD) and control (PF) rats. Panel A displays basal ACh values and the increase rise in ACh during maze testing (Mean \pm SEM). Panel B is the mean percentage of change from basal ACh levels that occurred during maze testing (Mean \pm SEM). Panel C is the positive correlation between alternation score and mean percent increase in ACh during maze testing. The gray squares are the data from the PTD-treated subjects whereas the black squares are data from the PF subjects.

rats exposed to PTD have a blunted hippocampal ACh release profile when behavioral tested using a spontaneous alternation task. These results suggest that diencephalic damage down regulates hippocampal ACh activation under certain environmental demands. However, the neuropathology produced by PTD model is not restricted to the diencephalon and limbic regions (Mair 1994; Langlais et al. 1996; Pitkin and Savage 2001). The midline thalamic nuclei that are damaged by PTD-treatment project to the striatum and cortex (Mair et al. 2002). Thus, the behavioral impairment produced by PTD treatment could be a result of the disruption of processing in numerous brain regions beyond the hippocampus (i.e., striatum, cortex). Therefore, the PTD model is limited in what it can tell us about the direct interrelations between the diencephalon and the hippocampus. However, the current study provides a starting point for understanding the relationships between interconnected memory-related regions in the rat brain. Studies assessing the direct interaction between thalamic and hippocampal systems are needed as well as those assessing the interactions between thalamic, striatal, and cortical regions.

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