THE POTENTIAL ROLE OF THIAMINE IN THE PATHOGENESIS AND TREATMENT OF ALZHEIMER'S DISEASE

BY

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A Thesis
submitted to the Faculty of Graduate Studies
in Partial Fulfilment of the Requirements
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MASTER'S OF SCIENCE

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FACULTY OF GRADUATE STUDIES

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PREFACE

In 1993, I entered graduate school with the desire to do research in the area of the effect of diet on behavior. I discovered a research paper which looked interesting. In 1992, a small study involving Department staff had suggested the possibility of a secondary thiamine deficiency in Alzheimer subjects.[1] A relationship of impaired biochemical thiamine status to cognitive decline was also suggested. Curious as to the ramifications of a thiamine deficiency, and the potential for thiamine supplementation, I proceeded to search the literature. The search was more fruitful than I ever imagined. This thesis documents my findings.

[1]Agbayewa, M. O., Bruce, V. M., Siemens, V. (1992). Pyridoxine, ascorbic acid and thiamine in Alzheimer and comparison subjects. Can. J. Psychiatry 37:661-662.

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ABSTRACT

The prevalence of Alzheimer's Disease (AD) is expected to triple by the year 2050. The abnormalities in biochemistry, clinical signs and symptoms and brain pathology in this most common form of dementia have been extensively documented. Primary research focus is on acetylcholine and amyloid abnormalities. The possibility of a secondary thiamine deficiency in this disease has been suggested by recent nutrition studies but the findings are difficult to interpret. From a literature search, this thesis documents evidence of a role for thiamine in the pathogenesis and treatment of AD. Further clinical investigations are warranted.

Dedication

To new horizons in the fields of nutrition science and Alzheimer research

Epigraph

Great turning points in life are not events but moments of illumination....

Emerson

INTRODUCTION

Alzheimer's Disease (AD) was described in 1907 by a German physician, Alois Alzheimer (1) and is now recognized as an increasing major health problem and the most common form of primary dementia (2). The disease, occuring in middle or later life (3), is characterized by an insidious onset and a progressive intellectual deterioration with three distinguishing features in autopsy brain tissue: neurofibrillary tangles, neuritic plaques, and granulovacuolar degeneration (4). In rare cases the disease follows an inheritance pattern (familial or FAD). The majority of cases appear to be sporadic (5). AD currently affects more than a quarter of a million Canadians (6) and approximately 4 million Americans (2). If no means of effectively preventing or treating the disease is discovered, the prevalence of AD is expected to triple by the year 2050 (7).

Two important areas of research in AD are abnormalities in acetylcholine (ACh) metabolism (8) and amyloid production (9). The focus on a cholinergic deficit stems from the important role of ACh in learning and memory and that it was the most severe, extensive and specific of many documented abnormalities (10). This deficit occurs at a relatively early stage of AD (11). Another early and critical event in AD is progressive deposits of amyloid in senile plaques and blood vessels in brain tissue (10).

The focus on specific important changes in this disease state has produced new detailed information but no unitary theory to account for the entire span of abnormalities has been proposed.[1] The relationship of the many biochemical and pathophysiological

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[1]The primary risk factors for AD are increasing age, APOE4 allele, and in rare familial AD, mutations in genes on chromosome 21(ß-amyloid, precursor protein), chromosome 1 (presenilin 2) and chromosome 14 (presenilin 1) (14). For further background on Alzheimer's Disease see references 2,5,12,13,14.

abnormalities documented in Alzheimer's Disease to nutrient metabolism has received little attention. If recent findings in AD are considered in the light of the biochemical as well as clinical and pathological changes that occur in thiamine deficiency states in animal and human studies, a new perspective on the possible pathogenesis of this disease unfolds. Moreover the potential of appropriate thiamine supplementation as an effective treatment looks exciting.

What is thiamine and what is its role in metabolism? What are the biochemical changes that occur in models of thiamine deficiency? What is the thiamine nutritional status of AD subjects?

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PART ONE. THIAMINE

CHAPTER 1

THIAMINE AND ITS ROLE IN METABOLISM

Background

Thiamine is an organic micronutrient obtained exclusively from the diet (1). Its name comes from the thio (sulphur) and amine (-NH2) groups in the molecule (2). It was originally discovered in response to a need to cure beriberi, a disease that became a public health problem of immense proportions where people consumed large quantities of polished rice at the turn of the century. This diet was deficient in thiamine for by polishing rice the thiamine-rich bran or outer coating was removed (3).

Sources

The richest dietary sources of thiamine are now known to be pork and whole/enriched grain products. It is also found in a wide variety of other foods including organ meats, yeast, leans meats, eggs, green leafy vegetables, nuts and legumes (4).

Thiamine Requirements for Elderly

In Canada, the Recommended Nutrient Intake for thiamine was established at 0.40mg./1000 kcal in 1990 (5). This standard was based on studies on adults and was considered to meet the requirements of almost all healthy individuals from infancy to old age. It was noted that requirements may be higher in older adults (6) but there were insufficient data upon which to base a different recommendation. It is interesting to note that this level of intake was also recommended by the majority of countries around the world (5).

Dietary Reference Intakes for thiamine were established in 1998 by a joint committee

of Canadian and American scientists (7), and are intended to replace the Recommended Nutrient Intake values. For adults ages 51 and older, the committee has recommended an EAR (Estimated Average Requirement) for thiamine of 1.0 mg/day for males; 0.9 mg/day for females. Recommended Dietary Allowances (RDA) values intended to meet the daily requirements for thiamine of most healthy individuals in this age group have been set at 1.2 mg/day for men; 1.1 mg/day for women. Again the standards for younger adults and elderly are the same.

Requirements for thiamine are known to increase with increasing carbohydrate intake and in hypermetabolic states such as hyperthyroidism, fever, and muscular activity (8).

Role in Metabolism

Thiamine plays a critical role in activating pyruvate dehydrogenase (PDHC), and α-ketoglutarate dehydrogenase (α-KGDHC), key enzymes of glycolysis and the TCA cycle (figure 1) .

In this function thiamine pyrophosphate acting as a coenzyme is essential for the oxidative decarboxylation of pyruvate and α-ketoglutarate (1).

PDHC

pyruvate + CoA + NAD+ -------> acetyl CoA + CO2 + NADH

α-KGDHC

α-ketoglutarate + CoA + NAD+ -------> succinyl CoA + CO2 + NADH

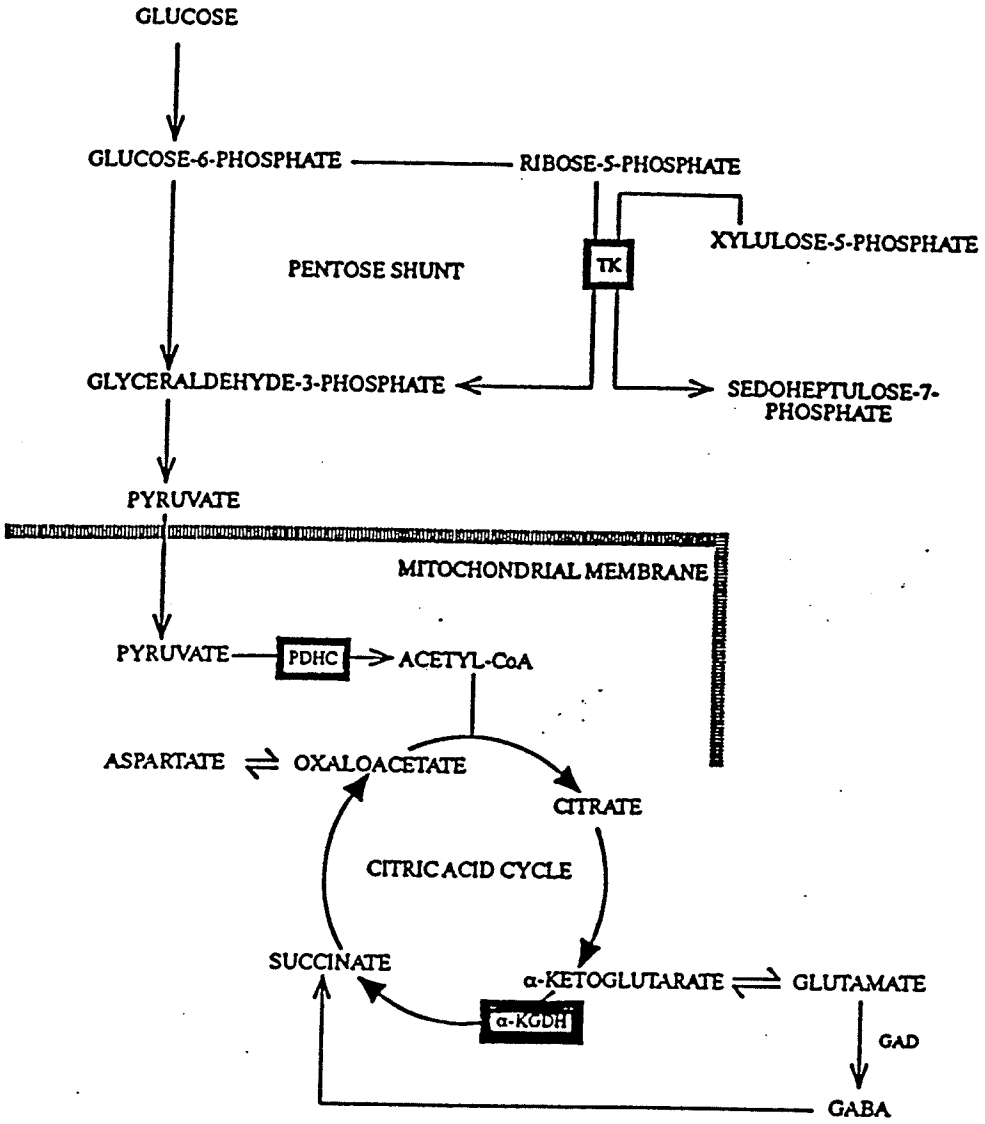

Figure 1. Thiamine-dependent enzymes.

Codes: CoA=coenzyme A; GAD=glutamic acid decarboxylase; TK=transketolase; PDHC=pyruvate dehydrogenase; α-KGDH=alphaketoglutarate dehydrogenase. GABA=γ-aminobutryric acid

Adapted from:Butterworth, R.F., Kril, J. J., Harper, C. G. (1993). Thiamine-dependent enzyme changes in the brains of alcoholics:Relationship to the Wernicke-Korsakoff Syndrome. Alcoholism:Clinical and Experimental Research 17:1084-1088.

Thiamine pyrophosphate (TPP) also acts as coenzyme in the pentose phosphate pathway in transketolase (TK) reactions (figure 1).

transketolase

Xylulose 5-P + ribose 5-P <----------> sedoheptulose 7-P + glyceraldehyde 3-P

In this role thiamine is involved in the synthesis of products of the pentose phosphate pathway, nicotinamide adenine dinucleotide phosphate (NADPH) and ribose (1). There is evidence that thiamine is related to another product of this pathway, reduced glutathione (9,10).

Thiamine plays an essential role in membrane and nerve conduction (11). Thiamine is located in nerve membranes and mitochondria (12) and is released by excitation of peripheral nerves (13). The finding that thiamine phosphorylated derivatives are associated with the sodium channel protein has led to the hypothesis that thiamine triphosphate plays a fundamental role in the control of sodium conductance at axonal membranes (14). Thiamine deficiency leads to reduced conduction velocity and increased axonal transport (15).

Research has demonstrated that thiamine is necessary for the biosynthesis of proteins (16), DNA (17,18), RNA (19,20), fatty acids (21) and cholesterol (21).

Thiamine is also important for the normal functioning of several neurotransmitters including histamine (22,23), and norepinephrine (24) as well as acetylcholine, gamma-aminobutyrate (GABA), glutamate, aspartate, and serotonin (11).

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CHAPTER 2

BIOCHEMICAL CHANGES IN THIAMINE DEFICIENCY STATES

Biochemical changes occuring in thiamine deficiency can be studied in both animal and human models. In animal models deficiency can be induced either by a thiamine-free diet or by the administration of thiamine antagonists in combination with a thiamine-free diet (1). Pyrithiamin is a potent thiamine analog that has commonly been used. In humans, biochemical changes have been studied in subjects placed on very low dietary thiamine intakes or in known thiamine deficiency disease states such as beriberi (2) and Wernicke-Korsakoff Syndrome (2,3,4).

Table 1 summarizes biochemical changes documented in these models of thiamine deficiency. These have been selected based on their relevance to the topic of this paper.

A few of these changes deserve special comment. In Wernicke-Korsakoff Syndrome, striking reductions in cerebral blood flow involving both cortex and white matter are evident, particularly in temporal and parietal regions (5). Chronic alcohol abuse, in the absence of thiamine deficiency can reduce CBF by neurotoxic effects (5). If thiamine deficiency is also present, more severe and localized blood flow reductions are observed (5,6).

A major metabolic consequence of a thiamine-depleted diet in the rat is a widespread decrease in cerebral glucose utilization which appears to be related to the declining thiamine content of various brain tissues (7).

Table 1. - Biochemical Alterations in Thiamine Deficiency Models

	References	
	Rodent	Human
↓ cerebral blood flow		(WK-5,6)
↓ cerebral glucose oxidation	(7,14)	
↓ synthesis of brain ATP	(15)	
disorder in synthesis of		
DNA	(16,17)	
RNA	(18,19)	
protein	(20)	
early cholinergic deficit	(21-24)	
↓ acetylcholine synthesis	(14,24,25)	
↓ serotonin uptake	(26-28)	
↑ RBC choline levels		(WK-29)
↓ TK activity in		
fibroblasts		(WK-8)
RBCs	(30,31)	(WK-9,31,32)
brain	(33-35)	(WK-36)
transketolase abnormality in		
fibroblasts		(WK-8,37)
RBCs		(WK-9)
↑ Km TPP		(WK-38)
↑ ETK-AC		(WK-38)
↑ histamine in hypothalamus	(39,40)	
↓ brain cholesterol	(41)	
↓ brain phospholipids	(41)	
↓ plasma thiamine	(42)	
↓ brain TPP	(43-46)	
↓ activity brain α-KGDHC	(14,47-49)	(WK-36)
↓ activity brain PDHC	(47,49,50)	(WK-36)
altered APP metabolism	(51-54)	
alteration in blood-brain barrier	(55,56)	(WK-57)
neuronal apoptosis	(58)	

Code: ETK-AC= erythrocyte transketolase activation coefficient
APP= amyloid precursor protein
WK= Wernicke-Korsakoff syndrome

A transketolase abnormality has been documented in Wernicke-Korsakoff disease (8,9). Recent evidence shows the TK enzyme protein becomes unstable when deprived of its TPP cofactor (10,11). The enzyme protein is changed into forms which either cannot be reactivated with thiamine administration or can only be reactivated with difficulty (11,12). It has been suggested that this does occur in thiamine deficiency (11,12). This explanation of the abnormality in TK in Wernicke-Korsakoff disease is further supported by a recent study which found no evidence for different TK alleles, tissue-specific TK isozymes, or differential mRNA splicing in TK derived from fibroblasts of Wernicke-Korsakoff subjects (13).

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PART TWO.

IS THERE EVIDENCE OF THIAMINE DEFICIENCY IN ALZHEIMER'S DISEASE?

CHAPTER 3

THE THIAMINE NUTRITIONAL STATUS OF ALZHEIMER SUBJECTS

There are serious challenges in assessing the thiamine nutritional status of Alzheimer subjects. The selection of appropriate subjects is critical and interpretation of study results is difficult.

An accurate diagnosis of Alzheimer's disease is essential to a well designed nutrition study on subjects with this disease. Because a definite AD diagnosis can only be confirmed by neuropathological study (usually postmortem), clinical diagnosis is still merely by exclusion (1). In addition there is a clinical variability of symptoms confounded by a considerable overlap with symptoms of other dementing conditions. In spite of these difficulties various clinical criteria sets have been established but often inadequately validated (1). Two sets of criteria that have been validated by autopsy studies are the DSM-III (2)[1] and the NINCDS-ADRDA (1). Nutritional studies using these diagnostic criteria have been conducted and include both dietary (3,4,5) and biochemical evaluations (3,5,6,7,8).

Dietary Assessments

Three dietary assessments of community living AD subjects have been reported (3,4,5). One study (4) compared the dietary intakes of 29 healthy controls and 35 moderately impaired community living AD subjects diagnosed by NINCDS-ADRDA criteria. Control subjects or AD caregivers completed a 3-day food record. Dietary intakes did not differ significantly between controls and AD subjects for 32 nutrients analyzed including thiamine. Both groups met RDA guidelines for thiamine intake. No biochemical assessment of

[1]DSM-IV criteria are also currently validated (29).

thiamine status was conducted. The authors concluded that moderately-impaired community dwelling AD patients do not differ from healthy controls in nutritional intake.

Two other studies on dietary intakes in community living AD and control subjects have been conducted (3,5). AD subjects met DSM-III diagnostic criteria for primary dementia. Caregivers or controls completed 3-day food records. Dietary intakes of thiamine did not differ significantly between controls and AD subjects (3,5). Means for thiamine intake in both groups exceeded 67% of the RDA (3) or met RNI standards (5). Biochemical measures of thiamine status were also taken and will be discussed in the next section.

The results of these studies (3,4,5) suggest that community living AD patients do not differ from healthy controls in thiamine intake.

Collection and interpretation of dietary intakes in AD subjects is challenging. In the dietary studies (3,4,5) caregivers were instructed to keep food intake records for the AD subjects, while age-matched controls kept their own records. The quality of the data obtained in these studies requires critical review. Elderly caregivers and/or controls may have been asked to document this dietary information. Errors in estimates of dietary intake are influenced by the elderly person's education, recent memory, and knowledge of what foods are used in the preparation of various menu items (9). The validity of self-reported dietary information probably diminishes with increasing respondent age (10), and there is a need for additional investigations on the validity of surrogate dietary information (10). Moreover, there is a concern that when people are asked for information on their food intake, they will change their eating habits or will record what they think they should have eaten rather than their actual diet (11).

Even with the most careful dietary data collection procedures, interpretation of results requires special consideration. The dietary intake record represents only a small window of time and the variability in the eating habits of AD subjects from day to day may be greater than in the healthy elderly population (see Table 2). More food record days may be required in

this population to assess dietary adequacy. It is known that AD subjects develop bizarre food habits as the disease progresses (12) which could rapidly impair biochemical nutritional status. Dietary intake data were analyzed for nutrient content and compared to RDA and RNI standards which were not intended for use in elderly with chronic or acute disease (9,13). The nutrient requirements of AD subjects are unknown. Preliminary evidence suggests that nutrient requirements may increase in this disease (14,15). A study of AD subjects in an active outpatient teaching program revealed an increase in reported food intake over a five year period with a significant concomitant weight loss (14). For these reasons, dietary intakes alone are a poor indicator of nutritional adequacy. In spite of these difficulties, dietary intakes have been measured as they can identify subjects with a great risk of nutritional inadequacies (11).

Table 2. - Nutritional Impact of Alzheimer's Disease

Disease Phase	Nutritional Problems
Early	Difficulty shopping, storing food, cooking Forget to eat or eat meals twice Preference for sweet and salty foods Unusual food choices
Middle	Increased energy requirements and weight loss Hoard food in mouth, fail to chew Lose ability to use utensils
Final	Unable to recognize food Refuse to eat Eat non-food items Unable to eat independently Require nasogastric feeding

Prepared from Gray, G. E. (1989) Nutrition and dementia. J. Am. Diet. Assoc. 89:1795-1802.

Biochemical Assessments

Biochemical assessments of thiamine status are employed to determine the level of thiamine tissue stores. The most common and widely accepted measure of thiamine biochemical status is erythrocyte transketolase activity (ETKA) (16,17). As this enzyme is dependent on thiamine pyrophosphate (TPP) for activity, measurement of ETKA is an indirect method of measuring erythrocyte TPP (ETPP) (18). TPP comprises 80% of the tissue thiamine stores (19) and the erythrocyte has been shown to be a good indicator of these body stores as it depletes at a similar rate to major organs (20). In a rat study it has been shown that the changes in ETPP after 5 days of thiamine deficiency closely resemble the drop in TPP seen in heart, liver, and brain (18).

The transketolase activity in haemolyzed erythrocytes is measured either by disappearance of pentose or appearance of hexose (21). ETK activity is measured *in vitro* before and after TPP is added and can be expressed in terms of ETK activity (ETKA), or the difference between the basal and stimulated measurements as a percentage of the basal activity (ETK-AC or TPP effect). In thiamine deficiency ETKA falls and ETK-AC rises (16).

Studies on ETKA (3), ETK-AC (7) and the TPP effect (5) have been conducted on AD subjects. In one study two methods of measuring ETKA were employed producing inconsistent results difficult for the investigators to interpret (3). The studies on ETK-AC (7) and TPP effect (5) both reported impaired thiamine status in AD subjects meeting recommendations for dietary thiamine intakes. Increased ETK-AC in NINCDS-ADRDA diagnosed AD subjects compared to controls on similar thiamine intakes and medications ($p<.05$) was reported (7), and increased TPP activity in DSM-III diagnosed AD subjects compared to controls with similar thiamine intakes ($p=.04$) (5). These last studies (7,5) suggest a secondary thiamine deficiency in AD i.e., a deficiency not due to inadequate intake but due to poor absorption, decreased utilization, impaired transport, increased excretion, thiamine destruction or increased requirements.

There is a difficulty associated with using ETKA, ETKA-AC or TPP effect to measure thiamine status in AD, however. In this disease, reduced affinity of erythrocyte transketolase for TPP, i.e. increased Km TPP has been reported ($p<.01$) (7,22), possibly associated with a structural abnormality of ETK (7,23,24). Measures based on ETK activity may not be valid indicators of TPP stores in this disease state. The usefulness of direct measures of ETPP by HPLC (25,26) may need to be assessed.

Other measures of biochemical thiamine status have been used in research on AD subjects. Low plasma levels (8) and normal blood levels of thiamine (6) have been reported. Neither of these measures has proved to be a sensitive index of thiamine deficiency (27,28). Low plasma levels of thiamine may reflect low nutrient intakes (28) and no dietary information was recorded in the study that found low plasma thiamine levels in AD subjects (8). Blood levels of thiamine may decrease very little in the course of thiamine deficiency and do not accurately reflect the state of the tissue stores (27).

Clearly it is difficult to conclude that either a primary or secondary thiamine deficiency occurs in AD based on current nutrition studies. At some stage of the disease process with the development of bizarre eating habits the potential for a primary thiamine deficiency exists. The need for more research into the cause of a likely secondary thiamine deficiency in this disease is the subject of this document.

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CHAPTER 4

SIMILAR BIOCHEMICAL CHANGES IN ALZHEIMER'S DISEASE AND THIAMINE DEFICIENCY

Studies on thiamine status have not provided clear information pointing to a potential role of thiamine in the pathogenesis or treatment of AD. Insight comes from the documented biochemical changes in AD and their similarity to those seen in thiamine deficiency states.

A multitude of biochemical abnormalities have been documented in AD. Studies have been conducted at all stages of the disease process on various tissues including cultured fibroblasts, blood, and autopsy and biopsy brain samples. As outlined in Table 3, AD has systemic manifestations. Of considerable interest is the marked reduction in activity of the thiamine pyrophosphate-dependent enzymes PDHC, α-KGDHC and TK in AD autopsy brain samples compared to controls matched for age, sex, and postmortem time (1-7). These studies report reductions in activity ranging from less than 30 to 70% for PDHC, less than 45% or more for transketolase, and less than 70% or more for α-KGDHC. Research has shown that PDHC (5) and α-KGDHC (3,7) activity are reduced in both histologically affected and unaffected regions. PDHC is antigenically and electrophorectically normal but present in reduced amounts (5). Polymorphisms of the α-KGDHC core component (E2k) have been reported in some patients, but no pathogenetic mutation (8). Reduced amounts of α-KGDHC protein subunits have also been reported (8). The decreases in α-KGDHC activity are generally larger than the decreases in enzyme protein (2). In AD autopsied brain tissue the activity of another mitochondrial enzyme, glutamate dehydrogenase (2,4) is normal.

Table 3 - Biochemical Abnormalities in Alzheimer's Disease (AD)*

Biochemical Abnormality	References
↓ cerebral blood flow	(24-26)
↓ cerebral glucose oxidation	(27-31)
↓ synthesis of brain ATP	(30)
disorder in synthesis of	
DNA	(32,33)
RNA	(34,35)
protein	(36,37)
early cholinergic deficit	(38)
↓ acetylcholine synthesis	(39-41)
↓ serotonin uptake	(38)
↑ RBC choline levels	(42)
↓ TK activity in	
fibroblasts	(3)
RBCs	(3)
brain	(1,3,4)
transketolase abnormality in	
fibroblasts	(3,43,44)
RBC	(1,3,45)
↑ Km TPP	(45)
↑ ETK-AC	(45)
↑ histamine in hypothalamus	(46)
↓ brain membrane cholesterol	(47-49)
↓ brain membrane phospholipids	(48,50)
↓ plasma thiamine	(51)
↓ brain TPP	(2,9,10)
↓ activity brain ∝-KGDHC	(2-4,7)
↓ activity brain PDHC	(4-6)
altered APP metabolism	(Rev. in ref.52 and 53)
alteration in blood-brain barrier	(54,55)
neuronal apoptosis	(Rev. in ref. 56)

*selected abnormalities have been chosen for the purposes of this paper

Of interest is the recent evidence suggesting reduced amounts of thiamine pyrophosphate (TPP) in this tissue (2,9,10). TPP is the major storage form of thiamine (11) and is depleted in the brain in thiamine deficiency states in animal models (12-16). The activity of TPP-dependent enzymes PDHC, α-KGDHC, and TK are also reduced in brain tissues in thiamine deficiency states in both animals and humans (17-23).

Reductions in brain metabolism in AD as measured by cerebral metabolic rate for glucose (CMR_{glu}) and for oxygen (CMR_{02}) and in cerebral blood flow (CBF) have been extensively confirmed and become more profound as the disease progresses (24). Early in the course of AD functional measures of brain activity (e.g. blood flow) have revealed hypometabolism in bilateral parietotemporal brain areas (25). Severe reductions in cerebral blood flow in this area occur in AD (27) as well as in Wernicke-Korsakoff Syndrome (see Chapter 2). In thiamine-depleted rats a widespread reduction in cerebral glucose utilization is related to the declining thiamine content of various brain tissues (see Chapter 2).

By comparing the selected biochemical abnormalities in AD and thiamine deficiency states (Tables 1 and 3) it becomes apparent that many of the same abnormalities have been documented. Is Alzheimer Disease a thiamine deficiency state? If so, one would expect clinical and pathological similarities as well.

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CHAPTER 5

THE LARGER PICTURE: CLINICAL SIMILARITIES BETWEEN THIAMINE DEFICIENCY STATES AND ALZHEIMER'S DISEASE

Generally clinical signs and symptoms are not considered a very objective assessment of a nutrient deficiency. The signs and symptoms are often non-specific and could be the result of many factors. However, clinical similarities between AD and thiamine deficiency states could shed a new light on the disease process.

The manifestations of thiamine deficiency in humans varies between disease states such as beriberi (1) and Wernicke-Korsakoff syndrome (1) and a diet-induced thiamine deficiency state (2,3). Moreover, clinical symptoms can also vary within each of these conditions (1-4). Many clinical variations have also been described in Alzheimer's disease as well (5). In light of this knowledge, the literature on both AD and TD in human, monkey and rodent models has been reviewed for typical and similar clinical manifestations.

Table 4 documents similarities between clinical signs and symptoms found in AD and thiamine deficiency in animal and human models. The NINCDS-ADRDA diagnostic criteria for Alzheimer's disease (6) include loss of memory, loss of weight, gait disorder, normal or slow EEG, depression, emotional and physical outbursts, altered sleep patterns, orientation disturbance, vision disturbance, hallucinations and in advanced disease increased muscle tone, myoclonus and seizures. Others (5,7-12,21) have reported these and additional clinical features of AD including confabulation and low blood pressure as well as specific memory and sensory deficits, and mood alterations. As indicated, each of these clinical signs and symptoms of AD have been documented in models of thiamine deficiency.

Table 4. - Similar Clinical Signs and Symptoms in Alzheimer's Disease (AD) and Thiamine Deficiency States (TD)

AD References	Sign/Symptom	TD References
(6)	↓ memory	(1,3,15,16)
(5)	↓ new learning	(1,17,18)
(5)	↓ remote memory	(18)
(6)	↓ weight	(2,3,18-20)
(6)	gait disorder	(1)
(5,6)	normal or slow EEG	(1)
(21)	↓ alpha power on EEG	(22)
(5-8)	depression	(2,3,17)
(5,8)	anxiety	(4,17)
(5,8)	apathy	(1-3,17)
(5)	irritability	(2-4)
(5)	↓ concentration	(1-3,17)
(5)	↓ interest in appearance	(1,3)
(5,6,8)	emotional or physical outbursts	(3)
(5)	crying spells	(3,17)
(5,6)	altered sleep patterns	(2,3,17)
(11)	olfactory deficits	(23,24)
(5,6)	orientation disturbance	(1,15,17)
(9)	low blood pressure	(2-4,17,19)
(10)	auditory system degeneration	(25,26)
(6,12)	vision disturbance	(1,17,20)
(6,7)	hallucinations	(17)
(5)	confabulation	(1,17)
	in advanced disease:	
(5,6)	increased muscle tone	(27)
(5,6)	myoclonus	(27)
(5,6)	seizures	(15,27)

There are also important differences between AD and certain TD states. For example, progressive intellectual deterioration is a key feature of AD (13) and Wernicke-Korsakoff syndrome (1) but is not a major feature of the common type of beriberi (1). In AD gait disturbances (6) and other neurologic abnormalities (5,6,14) typically occur in advanced stages; in Wernicke-Korsakoff syndrome these abnormalities occur early on (1).

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CHAPTER 6

SIMILARITIES IN BRAIN PATHOLOGY IN ALZHEIMER'S DISEASE AND THIAMINE DEFICIENCY STATES

The many documented similarities in biochemistry and clinical signs and symptoms between AD and TD would suggest a common brain pathology. Studies conducted on thiamine-deficient rodents, cats, and the rhesus monkey as well as humans with Wernicke-Korsakoff disease (W-K) have been reviewed for pathological changes in the brain which have also been documented in AD research.

A thiamine deficient diet administered to a variety of mammalian species readily induces lesions in the central nervous system (1). The severity and precise topography of the lesions depend upon variations in the experimental procedures and have been reviewed elsewhere (1,2).

Table 5 documents similarities in the brain pathology of AD and TD. Of particular interest is the similar pattern of neuroanatomical lesions that develop in AD and TD. Lesions in the mammillary bodies and the mediodorsal nucleus of the thalamus occur in AD (3,4) and are consistently found in W-K, a human model of thiamine deficiency (2). Severe cell losses have been reported in the nucleus basalis of Meynert in both AD (5-8) and Wernicke-Korsakoff Syndrome (7). Neurofibrillary tangle formation in this region has also been reported in AD (9,10) as well as Wernicke's Encephalopathy (11,12). In addition, lesions have been reported in the raphe nucleus and locus ceruleus in both AD (5,6,13-15)

Table 5. - Similar Brain Pathology in Alzheimer's Disease and Thiamine Deficiency States

AD References	Abnormality	TD References
(30)	cerebral atrophy	(37,38)
(36)	atrophy of cerebellum	(37,38)
(39)	widening of sulci	(1)
(39,40)	ventricular enlargement	(1)
	lesions in:	
(3,41)	mammillary bodies	(1,2,50,51)
(3,4)	dorsomedial nucleus of the thalamus	(1,2,50)
(39)	cerebellum	(1,2,52)
(39)	hippocampus	(2,23)
(5-8)	nucleus basalis of Meynert	(7)
(5,13,14)	raphe nucleus	(16,17)
(5,6,14,15)	locus ceruleus	(1,18,53)
(9,10)	neurofibrillary tangle formation in nucleus basalis of Meynert	(11,12)
(21)	evidence of damage to noradrenergic projection to cerebral cortex	(54)
(24,25)	degeneration of glutaminergic pathways	(22?)
(20,26)	possible loss/dysfunction of GABAergic neurons	(2,22,27)
(42,43)	loss of myelin	(1,2,17)
(39,44)	axonal degeneration	(31,32,55,56)
(45)	swelling of neuronal dendrites	(32,57,58)
(43)	spongiosis	(57,59)
(43,46)	glial cell proliferation	(2,32,60)
(46)	degenerative synapses	(32)
(47-49)	activation of brain macrophages	(2)

and TD (1,16-18,53). The nucleus basalis of Meynert, raphe nucleus, and locus ceruleus contain the cell bodies of cholinergic, serotonergic, and noradrenergic neurons respectively (19). Projections of these neurons are a major source of acetylcholine, serotonin, and norepinephrine in the cerebral cortex (20). In both AD (14,20,21) and TD (2,22,23) abnormalities in these neurotransmitter systems have been well documented. Abnormalities of the neurotransmitter glutamate have also been reported in AD (21,24,25) and TD (2,22,23). The loss of the integrity of glutaminergic nerve terminals has been documented in AD (24,25) and suggested in TD (22). In both AD (20,26) and TD (2,22,27) studies demonstrate regional

reductions in the brain concentrations of the neurotransmitter gamma-aminobutyrate (GABA) possibly associated with the selective loss and/or dysfunction of GABAergic neurons.

It should be noted that AD has pathological features which distinguish it from typical TD states. In AD, neurofibrillary tangles (NFT) are located in a variety of cortical and subcortical locations (28) but has, to our knowledge, have only been reported in one thiamine deficiency model (ie., in the nucleus basalis of Meynert in alcoholics with Wernicke's Encephalopathy (11,12)). Further studies may be required.[1] In AD senile plaques (SP) and granulovacuolar degeneration are a characteristic feature of neurons in the cerebral cortex and hippocampus (30). Senile plaques, to our knowledge, do not appear in the literature on TD, although there is some evidence of granulovacuolar degeneration (31,32). It should be noted that neurofibrillary tangles, senile plaques, and granulovacuolar degeneration are not unique to AD (33). Senile plaques and granulovacuolar degeneration can occur in the non-demented aged and tangles are found in a number of chronic degenerative brain disorders (33).

Some important relationships have been noted in AD research. The NFT and SP counts correlate with the deficits in major neurotransmitter systems (34). NFT counts in the nucleus basalis of Meynert are a stronger predictor of dementia than synaptic or neuronal loss (35). The magnitude of cerebellar atrophy correlates strongly with the duration and stage of AD (36). The pattern of regional hypometabolism parallels neuronal loss/atrophy, tangle formation, and synapse loss (61). As previously discussed, deficits in major neurotransmitters, tangles in the nucleus basalis of Meynert, cerebellar atrophy and similar patterns of regional hypometabolism occur in thiamine deficiency models.

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[1]The mean age of the patients with Wernicke's Encephalopathy was 57.9+/-9.1 (ref. 11) and 56.4+/-4 (ref. 12). Tangles were not seen in age matched controls (11). The incidence of NFT's is exponentially related to age and neuronal size in non-demented and Alzheimer subjects (29). Moreover the onset of neurodegeneration may be tightly programmed (29). Studies comparing tangle formation in age-matched elderly Alzheimer, Wernicke-Korsakoff and control subjects are needed. Brain areas that show a high incidence of tangles in AD should be examined, eg., entorhinal cortex, and hippocampus.

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PART THREE.

IS THERE A POTENTIAL FOR THIAMINE SUPPLEMENTATION IN ALZHEIMER'S DISEASE?

CHAPTER 7

PRELIMINARY THIAMINE SUPPLEMENTATION STUDIES IN ALZHEIMER'S DISEASE

In light of the many documented similarities in biochemistry, clinical signs and symptoms, and brain pathology between AD and TD states in animal and human models, what is the potential for effective thiamine supplementation in AD? Four thiamine supplementation trials have been reported in this disease state (1-4).

Blass and associates (1) conducted a double-blind, placebo controlled, crossover design study comparing the effects of 3 g./day of oral thiamine hydrochloride (THCL) for three months with those of a niacinamide placebo. Eleven moderately impaired subjects completed the study. Selection criteria included NINCDS-ADRDA diagnosis of "probable AD", no evidence of cerebrovascular disease, and well-nourished thiamine status as measured by TPP effect. Monthly physical examinations, Mini-Mental State Examinations (MMSE) (5), and behavioral ratings according to both Blessed et al. (6) and Haycox (7) were conducted. Global cognitive function, as measured by the MMSE scores, was slightly higher during 3 months with 3 grams of oral THCL per day than with the niacinamide placebo and the difference was highly significant ($p<.001$). Behavioral ratings, however, did not differ significantly, nor did the clinical state when it was judged subjectively. These results suggested a mild beneficial effect of oral THCL 3 g/day in AD.

Nolan and associates (2) conducted a double-blind, placebo controlled, parallel-group study comparing the effects of 3 g./day of oral THCL for twelve months with those of a lactose placebo. Ten subjects with "probable" or "possible" AD completed the study. Every three months a brief physical examination was conducted and a CERAD (consortium to

establish a registry for Alzheimer's disease) neuropsychological battery (8) was administered to each patient. The MMSE which was included in this battery of tests was defined as the primary efficacy measure. No significant differences were found between the placebo and thiamine groups at any point during the study. These results did not support the hypothesis that long term administration of oral THCL at 3 g/day would slow the progression of AD.

Meador and associates (3) conducted two experiments to assess the effect of high dose thiamine in AD. Their first experiment a double-blind, placebo controlled, randomized crossover design compared the effects of 3g./day of oral THCL with a lactose placebo for one month. Eighteen subjects with "probable" AD were enrolled. History, physical examination, and laboratory data (ie., CBC with indices and differential, SMA-18, B_{12}, folate, urinalysis) gave no evidence of malnutrition. Subjects were excluded from the study if they were taking concomitant medications with central nervous system activity, or if they had a history of alcohol or other drug abuse. At baseline and at the end of each one month treatment phase a physical examination, and neuropsychological tests including the Alzheimer Disease Assessment Scale (ADAS) (9) and the MMSE (5) were conducted. ADAS scores were better in thiamine than placebo conditions in 13 of 17 patients ($P \leq .0245$). Moreover, mean deterioration in ADAS score during thiamine treatment was 2.1 and during placebo was 6.7 points. The significance of this finding was not reported. The authors concluded that THCL at 3 g/day may have a mild beneficial effect on neuropsychological function in AD.

Meader's second experiment was conducted on 17 AD subjects meeting the same clinical criteria. Treatment with oral THCL was incrementally increased from 3 or 4 g/day up to a maximum of 5, 6, ,7, 7.5 or 8g/day over a period ranging from 2 to 13 months. MMSE scores did not significantly change across the entire study. ADAS scores did improve significantly ($P<0.05$) compared to baseline at 4 gm., 6.5 gm., 7 gm. of thiamine/day with a trend for improvement at 5 gm.. The authors concluded that thiamine may have mild beneficial effects in AD at these higher dosages. Side effects of nauseau and indigestion did

develop in two subjects at dosages of 7 and 7.5g/day.

Mimori and associates conducted a twelve week open trial of oral thiamine tetrahydrofurfuryl disulphide (TTFD), 100mg./day, on 9 subjects meeting both DSM-III/R criteria for dementia of the Alzheimer type and NINCDS-ADRDA criteria for "probable" AD (4). At baseline and at weeks 4, 8, and 12, scores were obtained on the Hasegawa Dementia Scale (HDS) (10), the MMSE (5) and the modified GBS(11). Blood levels of thiamine were measured before and after the trial using high performance liquid chromatography. After 12 weeks of TTFD therapy, scores on the emotional subscale of the GBS improved significantly ($p<.05$), there was a slight but significant improvement in the mean MMSE score ($p<.05$), and a tendency toward mild improvement in the total GBS scale ($p<.01$). There was no significant difference in the HDS. Of the nine subjects only those who were mildly impaired showed improvement. Blood thiamine levels were within the normal range before the study (mean 32.5+/-11.3ng./ml) and increased markedly after the 12 weeks (to 257.4+/-99.4ng./ml.).

Three of these studies suggested a mild beneficial effect of thiamine in AD (1,3,4). One study found no treatment effect (2). Some potential for treatment with thiamine in this disease state has been established by these trials. It is interesting to observe that AD subjects with "well nourished" thiamine status as determined by TPP effect, responded to thiamine supplementation (1). As previously discussed, this measure may not be a valid marker of thiamine stores in AD.

In three of the supplementation trials (1-3), oral THCL was administered in divided doses of 1 gram or more throughout the day. The amount that was actually absorbed is unknown. Man has a rate limited capacity to absorb oral thiamine hydrochloride (12). An early study found an excessive amount of oral thiamine over about 5 mg. can not be absorbed in healthy persons in the fasting state (13). This limited absorption was also confirmed by a study which demonstrated a maximum absorption of 4.8 mg. following a 20 mg. oral dose in normal human controls (14). Moreover, based on studies in rats, aging has a detrimental effect

on thiamine absorption (15). As the absorption of oral THCL in AD subjects has not been studied and the thiamine requirement in this disease is unknown, including a biochemical measure of thiamine status in future studies may be beneficial. Correlations of these markers with outcome measures such as cognition or behavior scores would be most informative.

TTFD was administered in one short trial without a control group (4). This lipid-soluble derivative has been recommended for treatment of thiamine deficiency due to its lack of toxicity and high oral effectiveness (12,16,17). Although the results suggested a significant beneficial effect on cognitive function in mildly affected patients with AD, the possibility of a placebo effect cannot be excluded. Well-designed double-blind studies are needed to assess the therapeutic potential of TTFD in AD.

In the four supplementation trials (1-4), dietary intake received little or no attention. In two trials (1,3), the researchers stated that the patients were being cared for by devoted caregivers with a particular concern for nutrition. Dietary assessments were not conducted in any of the studies (1-4). In one study there was no measure of conventional biochemical indices of general nutritional status or thiamine status (2). Some researchers appeared to conduct these measures before the trial only (1).

For several reasons the diet of subjects should not be ignored in thiamine supplementation trials in AD. Thiamine does not function independently in the body. Its capacity to work metabolically is intrinsically linked with the ready availability of other nutrients such as folate, magnesium, calcium, niacin, riboflavin, vitamin B12, and vitamin B6 (18-22). Moreover the deficiency of other nutrients can have a deleterious effect on memory, an important aspect of cognitive functioning which is often being measured as an outcome variable. These include iron, zinc, iodine, and omega-3 fatty acids (23-25). Thus, if subjects in thiamine supplementation trials were not consuming adequate levels of other nutrients both the ability of supplemental thiamine to function metabolically and the outcome measure of cognitive functioning scores could be adversely affected.

There is more evidence that the dietary intakes of AD subjects should not be ignored in thiamine supplementation trials. Bizarre eating habits develop in AD (26) concurrent with the deterioration in memory, judgement and the ability to recognize and detect odors. Moreover, the elderly often have reduced intakes and absorption of several nutrients including calcium and vitamin D (27). Low erythrocyte concentrations of magnesium (28), and reduced intakes of riboflavin (29) have also been reported. This suggests a high risk for nutrient deficiencies in the AD study population.

Thiamine absorption can be seriously jeopardized by concurrent alcohol consumption (18). Two of the thiamine supplementation trials did not screen for this factor (2,4). Large amounts of tea (8 cups or more per day) will significantly decrease the availability of thiamine in food eaten with the tea (30). Tea consumption was ignored in these trials (1-4). Other foods also contain factors which reduce the bioavailablity of thiamine. These include betel nuts, raw fish, and shrimp (31), as well as coffee (32), blueberries, blackcurrents, brussel sprouts, and red cabbage (33).

In these studies as well (1-4) concurrent disease states, medical conditions and medications received little (1,3,4) or no attention (2). Numerous medications can effect cognitive functioning (34) and the ability to consume, absorb and metabolize nutrients (35) (see Appendix A re: thiamine). Moreover several disease states and conditions can influence thiamine metabolism (see Appendix B). Medical conditions can influence the ability of subjects to eat, digest and absorb food (35). To clearly understand the potential effect of thiamine supplementation in AD, study subjects should be screened and monitored for factors which can interfere with thiamine status and cognitive functioning. Nutritional counselling and/or the administration of a multivitamin-mineral supplement together with the thiamine supplement may be beneficial.

In the four trials (1-4) the MMSE was utilized to assess cognition. Studies have shown that MMSE scores can be influenced by age, education, and cultural background (36).

Moreover the MMSE has been criticized for its lack of sensitivity to mild cognitive impairment and to progressive changes ocurring with severe AD (36). Although subjects acted as their own controls (1-4), another measure such as the ADAS-Cognitive section may be more suitable for assessing improvements in cognition with thiamine trials. The ADAS-C has been shown to be effective for assessments at all stages of AD (37), is only minimally affected by age and education (38), and was designed to measure the effects of drugs given to improve cognition associated with AD (39). Two of the thiamine supplementation trials showed no treatment effect with MMSE (2,3), yet one of these trials did detect an improvement in cognition with ADAS (3). Correlating AD patient scores on sensitive measures such as the ADAS-C with biochemical measures of thiamine stores would improve the design of future studies on thiamine supplementation in AD.

Out of the four AD thiamine supplementation trials (1-4), only three monitored subjects for evidence of thiamine toxicity (1,3,4). As toxic effects were noted in one study (3), future trials should include monitoring for these effects.

Conclusion

Three out of four preliminary AD thiamine supplementation trials have suggested a mild beneficial effect of thiamine in this disease (1,3,4). In future trials subjects should be screened and monitored for factors which can interfere with thiamine status and cognitive functioning. Sensitive measures of cognition should be used and results correlated with a biological marker of thiamine status to determine a cause-effect relationship. When high dose thiamine is administered, subjects should be monitored for signs of toxicity.

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CHAPTER 8

REVERSIBILITY OF THIAMINE DEFICIENCY ABNORMALITIES

To appreciate the potential impact of appropriate thiamine supplementation in AD, it is necessary to consider the reversibility of biochemical and clinical abnormalities documented in TD states in human and animal models.

Reversible and partially reversible abnormalities in TD are listed in Table 6. In each of the referenced studies either thiamine deficient humans or animals have demonstrated normalization or improvement of a parameter in response to thiamine supplementation. The parameters considered in Table 6 only include those that have also been documented in AD. As indicated, improvements or normalization of cerebral blood flow (1,2), cerebral glucose oxidation (3), DNA synthesis (4), transketolase activity in red blood cells (5) and brain tissue (6), and brain α-KGDHC (3,7) and PDHC (8) activity have resulted from thiamine supplementation in thiamine deficient models. The synthesis of acetylcholine (3), and the levels of histamine in the hypothalamus (9) have also been normalized.

Some other abnormalities in neurotransmitter function which occur in TD rat models can also be reversed with thiamine supplementation. These include impaired serotonin uptake in cerebellar synaptosomes (10), increased endogenous 5-HIAA levels in the medulla-pons (11), reduced GABA concentrations in cerebellum and pons (12), reduced catecholamine turnover in cerebral cortex, brain stem, and cerebellum (13), and reduced GLU and ASP in cerebral cortex and pons (14). Because they occur in different brain regions or have not been consistently documented in AD they are not included on the table.

Table 6. - Abnormalities in Alzheimer's Disease that are Reversible in Thiamine Deficiency Models

Biochemical:	References
↓ cerebral blood flow	(1*, 2(*))
↓ cerebral glucose oxidation	(3*)
disorder in synthesis of DNA	(4*)
↓ acetylcholine synthesis	(3*)
↓ TK activity in	
RBCs	(5*)
brain	(6(*))
↑ histamine in hypothalamus	(9*)
↓ activity brain ∝-KGDHC	(3*,7*)
↓ activity brain PDHC	(8*)

Sign/Symptom	References
↓ memory	(17*,24*,15(*))
↓ new learning	(19*,15(*))
↓ weight	(16*)
gait disorder	(15(*))
depression	(17*)
apathy	(15*,17*,18*)
↓ interest in appearance	(17*)
altered sleep patterns	(17*,19*)
orientation disturbance	(19*,20*)
low blood pressure	(19*,21*)
auditory system degeneration	(22*,23(*))
vision disturbance	(19*,15*,24*)
confabulation	(15*,19*)

* = reversible
(*)= not completely reversible

Of considerable interest is the improvement in clinical signs and symptoms seen with thiamine supplementation. Memory deficits resulting from thiamine deficiency can be improved. Following treatment of 104 Wernicke-Korsakoff patients with parenteral thiamine, 50 to 100 mg. daily, and a balanced, high caloric diet, 74% of the test group showed an improvement in memory (15). In 21% the recovery was complete. Except for a permanent

gap in memory for the period of their acute illness, these subjects could recall their past history, remember day-to-day events and learn new information. Nineteen out of 22 of these patients had a severe amnesic syndrome initially. Memory deficits are also a key feature of AD.

Other clinical signs of thiamine deficiency that can be normalized or improved with thiamine supplementation include weight loss (16), gait disorder (15), depression (17), apathy (15,17,18), loss of interest in appearance (17), altered sleep patterns (17,19), orientation disturbance (19,20), low blood pressure (19,21), auditory system degeneration (22,23), vision disturbance (15,19,24) and confabulation (15,19). These abnormalities have been documented in AD (see Table 4).

Is There a Potential to Reverse the Transketolase Abnormality in Thiamine Deficiency and Alzheimer's Disease?

The transketolase abnormality that occurs in red blood cells in TD (25,26) and AD (27-29) may also be reversible. Although some researchers have suggested that it may be difficult to reactivate the transketolase protein after it is converted into abnormal forms in thiamine deficiency (30-31) others have suggested that it may be possible (32). Preliminary evidence, according to these researchers suggests that alcoholics demonstrate high amounts of low affinity (damaged) transketolase enzyme. After two months of detoxification treatment the pattern of enzyme variants reverted almost to normal. The exact treatment protocol was not stipulated.

In AD research as well, treatment with high energy phosphates, piracetam, thiamine, pyridoxine and magnesium has been shown to reduce the elevated Km TPP or low affinity of erythrocyte transketolase for its cofactor TPP (33).

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CHAPTER 9

IS THERE A POTENTIAL FOR THIAMINE SUPPLEMENTATION TO CORRECT THE CHOLINERGIC DEFICIT IN ALZHEIMER'S DISEASE?

The cholinergic deficit is one of the most severe, extensive and specific of AD abnormalities (1) and remains a major focus of therapeutic research (2). This deficit occurs early in the course of AD (3,4). What is the nature of this deficit? What therapeutic drug approaches have been tried? What is the potential of thiamine supplementation to correct these abnormalities?

Acetylcholine Metabolism

To understand the changes underlying cholinergic neurotransmission in AD a review of the normal life cycle of acetycholine would be in order. The neurotransmitter is manufactured primarily in the nerve terminals from which it is released. Choline is delivered to the synaptic cleft by the blood and enters a presynaptic cholinergic terminal. Two transport proteins are involved in the uptake of choline; one has a very high affinity for choline and enables the terminal to take up almost all the choline available to it in the synaptic cleft. Once inside the cholinergic terminal choline can react with acetyl coenzyme A to form acetylcholine. The enzyme choline acetyltransferase (ChAT) catalyzes the reaction. As terminals have an excess of ChAT in relation to the amounts of choline and acetyl-CoA, the rate at which ACh is synthesized depends on the level of the two precursors. ACh molecules are stored in the terminal until the arrival of a nerve impulse discharges some of them into the synapse. The ACh molecule can then cross the synapse to interact with a receptor on the postsynaptic neuron thus transmitting the signal generated by the nerve impulse. It can instead interact with a receptor on the presynaptic membrane thereby modulating the further release of

ACh. Or it can be broken down by acetylcholinesterase (AChE), yielding choline, which is taken up by the terminal or carried off in the blood. The breakdown of phosphatidlycholine, a constituent of cell membranes contributes to the choline supply (5).

The Cholinergic Deficit in Alzheimer's Disease

In AD research the first major biochemical abnormality identified was the marked reduction of ChAT levels in the hippocampus and the cerebral cortex (5). Since that time, many studies have confirmed the relationship between the severity of AD and ChAT activity (6). This activity also correlates with plaque counts (1).

In AD, the nucleus basalis of Meynert in the basal forebrain, which sends cholinergic projections to the cerebral cortex has been shown to degenerate extensively (6-9).

Reductions in the synthesis of ACh in AD have also been observed. Although ACh is difficult to measure in the postmortem brain because of rapid postmortem deterioration (10), there is good evidence that radiolabelled ACh formed by biopsy mini-slices provide a representative measure of the amount of neurotransmitter synthesized (11). Biopsy samples of AD brain tissues have shown a reduced synthesis of ACh in frontal and temporal lobes compared to normal controls (12). Another study showed a significant correlation between an overall clinical assessment of the degree of dementia in AD patients who were biopsied, and [^{14}C]-acetylcholine synthesis (13).

In AD, reductions in ACh release have been observed (13-15). In AD cortical areas and hippocampus consistent losses in nicotinic receptors have also been reported (16). A certain proportion of nicotinic sites are located presynaptically and act as autoreceptors regulating ACh release (17). As nicotinic agonists stimulate brain ACh release (17), the reduction in ACh release may be related to the altered functioning or loss of nicotinic receptors.

Muscarinic cholinergic antagonists are very detrimental to AD patients. Various subtypes of muscarinic receptors have now been studied and there is evidence that M1

receptors, located primarily postsynaptically, are functionally disturbed in AD yet not reduced in number. M1 receptors stimulate phospholipase C, phosphokinase C and inositol triphosphate metabolism. The number of M2 receptors, predominately presynaptic, are consistently reduced in AD studies (18). M2 receptors act as negative autoreceptors to decrease brain ACh release (17).

In AD biochemical and morphological changes in the structures storing and releasing ACh have been observed (15). ACh in the terminals is stored in membrane-bound synaptic vesicles (19).

In AD, the form of ACHE important for the degradation of ACh at cholinergic synapses, tetrameric G4, is decreased in the neocortex and hippocampus and could reflect the state of degeneration of cholinergic terminals (20).

In AD it is confirmed from biopsy and rapid autopsy studies that high affinity uptake of choline into cholinergic terminals is deficient (21,22), especially in the hippocampus (21).

Cholinergic Drug Therapy in Alzheimer's Disease

Several types of drugs have been used in an attempt to correct these abnormalities in cholinergic transmission in AD. These include acetylcholine precursors such as choline and phosphatidylcholine (lecithin) to increase ACh concentrations, drugs to enhance ACh release, cholinergic agonists to directly activate postsynaptic target receptor sites, and acetylcholinesterase inhibitors to prevent the hydrolysis of synaptically released ACh. Results have been disappointing (23). Even the cholinesterase inhibitor Aricept does not stop or reverse the progression of AD (24) and does not act as an effective treatment of symptoms for all or even most patients (24). Aricept became the first drug approved for treatment of AD in Canada in 1997 (25).

AD researchers have been challenged by the limited success of cholinergic replacement therapy, the development of toxic side effects with various drug treatments, and the knowledge that AD is a disorder not only of acetylcholine but also multiple

neurotransmitter systems (23) including serotonin, norepinephrine, glutamate, aspartate, histamine and gamma-aminobutyric acid. Thiamine researchers have shown that thiamine is necessary for the normal functioning of each of these neurotransmitter systems (26-29). In what way could the cholinergic abnormalities in AD be related to thiamine metabolism? Are parallel changes observed in thiamine deficient models? Is there a potential for thiamine supplementation to correct this deficit? We will consider each of the documented cholinergic abnormalities in AD.

The Potential Role of Thiamine in the Pathogenesis and Treatment of Alzheimer's Disease Cholinergic Abnormalities

1. Early Cholinergic Deficit in Alzheimer's Disease

In thiamine deficiency a cholinergic deficit occurs early on (30-33). Thiamine deficient rats exhibit early deficits in string-test performance and staring behavior. These deficits can be manipulated by the administration of cholinergic agonists and antagonists (33).

2. Reduction in Choline Acetyltransferase Activity in Alzheimer's Disease

Although some research has suggested that the activity of choline acetyltransferase (ChAT) is not changed by thiamin deficiency (33,34), combining the effect of thiamine deficiency and aging appears to influence ChAT status in rodents (35,36). Compared to young rodents, aged rodents have fewer ChAT-positive cell numbers in the medial septum (35) and lower ChAT activity in whole brains (36). Pyrithiamine treatment potentiated these effects (35,36).

3. Degeneration of Nucleus Basalis of Meynert in Alzheimer's Disease

Loss of neurons in the nucleus basalis of Meynert has been demonstrated in Wernicke-Korsakoff Syndrome (WKS)(8). WKS is a thiamine deficiency state (37).

4. Reduced Synthesis of Acetylcholine in Alzheimer's Disease; Choline Not Effective

ACh synthesis is reduced in severe thiamine deficiency (33,38-40), even in the

presence of apparently adequate levels of ChAT and choline (40). Thiamine deficiency may reduce the availability of high energy phosphates produced by the TCA cycle or reduce acetyl-CoA production from impaired pyruvate dehydrogenase complex activity (PDHC) (38). The acetyl moiety of ACh in the brain is derived mainly from pyruvate (41,42). Impaired PDHC activity in the brain in a thiamine deficiency rat model has been shown to be reversible with thiamine administration (43). Normalization of impaired ACh synthesis in this model has also been demonstrated (39)

It is interesting to note that a reduction in PDHC activity has also been demonstrated in AD and appears to be related to the extent of the cholinergic deficit (44).

5. Loss of Nicotinic Receptors in Alzheimer's Disease and Reductions of Acetylcholine Release

The effect of thiamine deficiency on the numbers of nicotinic receptors does not appear to have been researched. There is evidence, however, that thiamine binds reversibly to nicotinic receptors (45), may be necessary for the function of presynaptic nicotinic receptors (45,46), and is involved in ACh release from the presynaptic junction (33,47-49).

6. Muscarinic Lesion in Alzheimer Disease

Although the density of muscarinic cholinergic receptors in thiamine deficient rats appears to be controversial (34,50), there is evidence of a central muscarinic cholinergic lesion in this model (33).[1]

7. Changes in Structures Storing and Releasing Acetylcholine in Alzheimer's Disease

Morphological studies carried out on the brains of thiamine-deficient rats show

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[1]Behavioral abnormalities in early stages of thiamine deficiency in pyrithiamin-treated rats include low string test scores and high staring scores. The muscarinic agonist arecoline was as effective as thiamine in improving both scores. Although physostigmine, an acetylcholinesterase inhibitor improved scores in a similar fashion, its effects were blocked by the concurrent administration of atropine, a muscarinic receptor blocker (33). Thus,in this model, thiamine deficiency acts like a muscarinic blocker and thiamine treatment like a muscarinic agonist. Administration of physostigmine concurrently with methatropine, a peripherally acting muscarinic receptor blocker, did not block the effect of physostigmine. The researchers concluded that this model demonstrated a central muscarinic cholinergic lesion (33).

hypertrophy of presynaptic boutons and a reduction in the number of synaptic vesicles (51,52).[2]

8. Reduction in Tetrameric G4 Form of Acetylcholinesterase in Alzheimer's Disease

Studies on thiamine deficient rats have demonstrated ACHE activity (33) does not decrease. In spite of this fact there is evidence that thiamine could have a beneficial effect on ACHE in AD. Researchers have been experimenting with ACHE inhibitors in AD to prevent the hydrolysis of ACh in the synaptic cleft. It has been demonstrated that thiamine can inhibit the activity of acetylcholinesterase (48). Thiamine at concentrations of 10^{-3}, 5 x 10^{-3}, and 10^{-2} M reduced the enzymatic activity of AChE of the Torpedo electric organ by 9, 13, and 45% respectively when 10^{-2} M-ACh was used as the substrate. A greater effect was observed when the substrate was used at concentrations lower than 10^{-2}. In AD, ACh synthesis is reduced. If thiamine supplementation in AD could increase the concentration of thiamine the activity of ACHE could be strongly inhibited.

A study conducted on albino mice suggests that thiamine pyrophosphate (TPP) can inhibit ACHE in the brain (53). There is recent evidence of a reduction of TPP in AD brain tissue (54-56) as well as in brain tissue from thiamine deficiency animal models (57-60). If thiamine supplementation could increase the levels of TPP in the brain of AD subjects this may also inhibit ACHE and prevent the hydrolysis of ACh in the synaptic cleft.

9. Decreased High Affinity Uptake of Choline in Hippocampus in Alzheimer's Disease

Although one study has demonstrated that high affinity uptake of choline is not reduced in thiamine deficiency (61), injections of a thiamine derivative, sulbutiamine, have been shown to increase high affinity uptake of choline in the hippocampus in non-deprived mice (62). Thiamine supplementation in AD may improve high affinity uptake of choline as

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[2]Rats fed a thiamine-deficient diet were selected for electron microscopic study in the early stages of the first acute symptomatic episode of deficiency. The fine structure of the lateral vestibular nucleus was examined (51).

well.[3]

Conclusion

Based on these findings and the growing evidence documented in this paper of a thiamine deficient state in AD, appropriate and early thiamine treatment in AD may potentially correct abnormalities in cholinergic transmission in AD. The synthesis of ACh, and release of ACh may improve, the breakdown of ACh in the synaptic cleft may be reduced, and the high affinity uptake of choline increased (see fig.2). Moreover, treatment with thiamine derivatives is non-toxic (63-65) and may improve or normalize the functioning of several other neurotransmitters including serotonin, norepinephrine, glutamate, aspartate, histamine and gamma-aminobutyric acid, as well as several clinical signs and symptoms of AD.

[3]Evidence to support thiamine's role in each of these individual aspects of cholinergic transmission comes from studies that demonstrate impairment of neuromuscular transmission induced by pyrithiamine and reversed by thiamine (45,46).

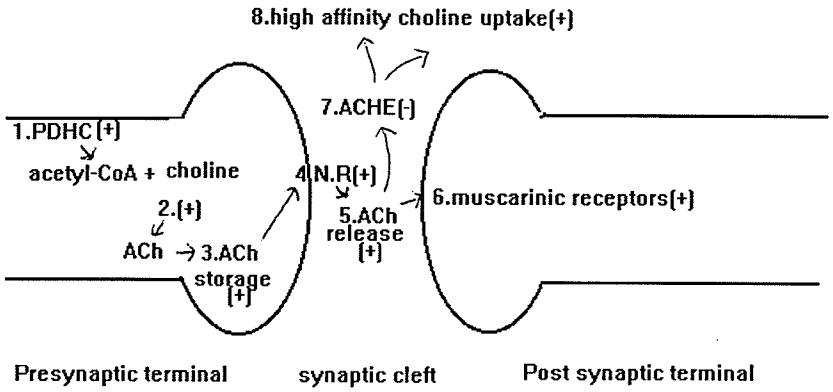

Figure 2. Thiamine's Role in Acetylcholine Metabolism

Thiamine:
1. promotes the activity of PDHC to produce acetyl-CoA.
2. promotes ACh synthesis.
3. promotes normal ACh storage.
4. may be necessary for the function of nicotinic receptors.
5. is involved in ACh release from the presynaptic junction.
6. is necessary for the functioning of muscarinic receptors.
7. inhibits the breakdown of ACh by inhibiting the activity of ACHE.
8. promotes high affinity choline uptake.
Codes: PDHC=pyruvate dehydrogenase complex; ACh=acetylcholine
References are in the text.

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CHAPTER 10

IS THERE A POTENTIAL FOR THIAMINE SUPPLEMENTATION TO CORRECT THE ABNORMALITIES IN AMYLOID PRODUCTION IN ALZHEIMER'S DISEASE?

Another key area in AD research is currently the mechanisms of abnormal amyloid production found in this disease state. Amyloid deposits in the brains of patients with AD contain a protein (beta A4) which is abnormally cleaved from a larger transmembrane precursor protein (APP) (1). BA4 amyloid protein is progressively deposited in senile plaques and blood vessels in AD brain tissue and appears to be an early and critical event (2-4).[1] Whether B-amyloid deposition in plaques is a cause or result of the nerve degeneration remains controversial (3,7).

A current therapeutic approach to correcting amyloid abnormalities in AD is outlined in figure 3. Amyloid precursor protein is embedded in the nerve cell's membrane, partly inside and outside of the cell (8). Proteases act on particular sites in APP, cleaving it into protein fragments (8). In a healthy brain, amyloid precursor protein is first cleaved by alpha-secretase near its base and then by gamma-secretase right at the base. The resulting short peptide is soluble (8) and harmless (9). This pathway is non-amyloidogenic (10). In AD, a beta-secretase initally cleaves the APP in a different spot so when the gamma-secretase later

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[1]Attention has been focussed on this protein and its role in AD pathology since the discovery that rare,early-onset forms of autosomal dominant AD are associated with mutations in the ß-amyloid precursor protein, presenilin 1 and presenilin 2(5). These genetic defects have all been linked with increases in the cerebral production or deposition of ß-amyloid peptides (4,5). In the much more common sporadic late-onset varieties of AD, amyloidogenesis occurs as well. Increased levels of ß-amyloid occur in only a minority of these cases however, and poor clearance of ß-amyloid or other factors are implicated(6). In both early-onset and late-onset AD the pathology is virtually identical(5,6) with both early and selective deposition of ß-amyloid and the formation of both neuritic plaques and tangles(6). Researchers suspect that similar pathways to pathogenesis are at work in both forms of the disease(6).

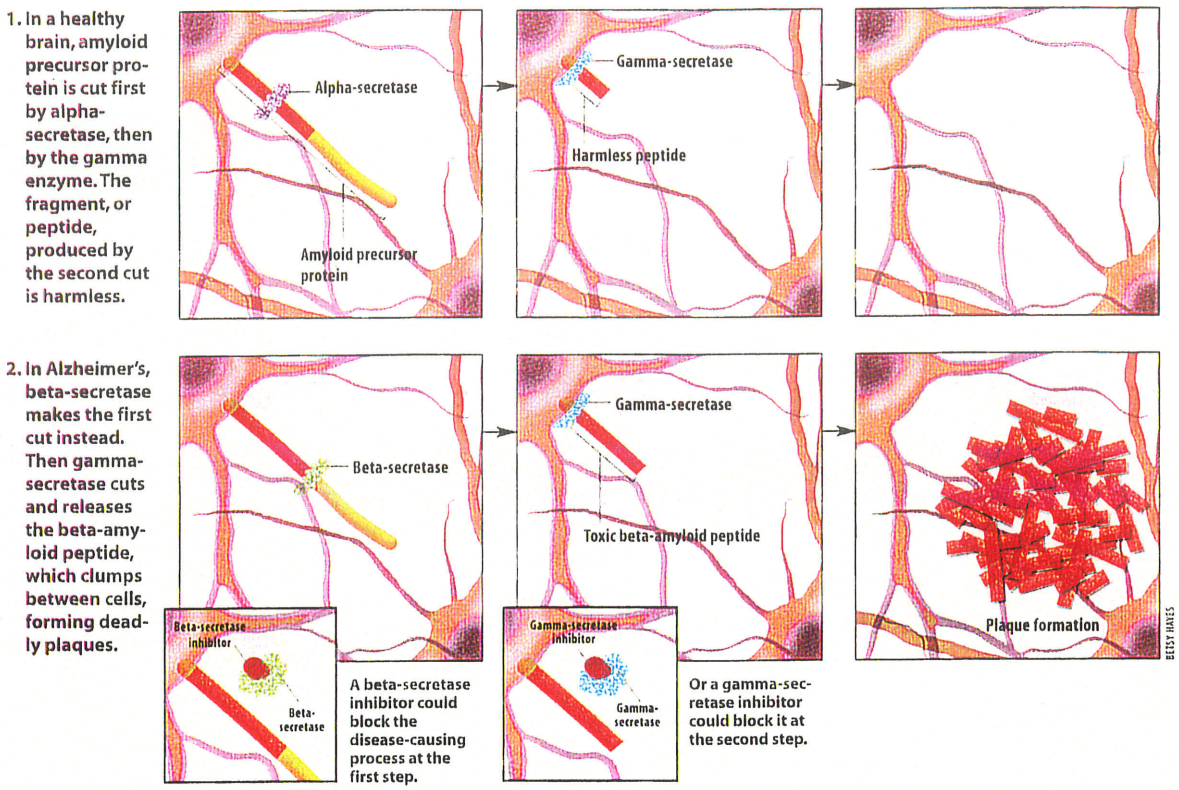

Figure 3. Therapeutic target of amyloid abnormality in Alzheimer's Disease
Source: Garber, K.(2001). An end to Alzheimer's? Technology Review 104(2):70-77.

cleaves the molecule at its base, the resulting fragment (ß-amyloid) is insoluble and forms clumps between cells known as plaques (9). This is an amyloidogenic pathway (10). Researchers are investigating beta-secretase inhibitors which could block ß-amyloid formation at the first step and gamma-secretase inhibitors which could block it at the second step (9).

Several lines of evidence suggest that thiamine may play a role in the pathogenesis and treatment of amyloid abnormalities in AD.

The Effect of Thiamine on AChE Activity

Several studies have suggested that AChE inhibitors alter the processing of APP (11). Very recently it has been demonstrated that reversible and irreversible AChE inhibitors promote the non-amyloidogenic route of APP processing which may be due to their stimulatory effects on protein kinase C. PKC activation may enchance the alpha-secretase activity (11).

As discussed in Chapter 9, thiamine can inhibit the activity of acetylcholinesterase (12). Thiamine's effect on protein kinase C does not appear to have been studied. It is plausible that thiamine may also promote the non-amyloidogenic route of APP processing due to its role as an AChE inhibitor.

The Possible Effect of Thiamine on ADChE Activity

B-amyloid protein formation and accumulation in plaques is intimately associated with high ACHE activity. Moreover this association already occurs at a very early stage of plaque formation (13). This form of AChE associated with plaques in AD (ADChE) possesses different enzymatic properties than the form associated with normal neurons and axons (14). ADChE appear to be inhibited by serotonin at concentrations that have no effect on the AChE of normal neurons. It has been suggested that ADChE's may act as proteases and help in the formation of plaques (14).

Thiamine can inhibit the activity of AChE (12). Whether thiamine can inhibit the activity of ADChE associated with plaques in AD is unknown. Thiamine may exert an indirect effect through its action on serotonin. Both impaired serotonin uptake (15) and increased endogenous levels of the serotonin metabolite 5-HIAA (16) can be normalized with thiamine administration to thiamine deficient rats. Impaired serotonin uptake has been observed in AD (17). Thiamine may increase serotonin levels in AD, inhibit ADChE, and reduce the activity of proteases that are involved in plaque formation.

The Effect of Thiamine on Muscarinic and Nicotinic Receptors

As discussed previously, preliminary evidence suggests that thiamine deficiency acts as a muscarinic receptor blocker and thiamine treatment as a muscarinic receptor agonist (18). Research has demonstrated that activation of muscarinic receptors can stimulate non-amyloidogenic processing of APP and in many cases concurrently inhibit amyloidogenic processing (10). Thiamine may activate muscarinic receptors and inhibit the production of ß-amyloid.

Thiamine binds to nicotinic receptors (19) and may also be necessary for their function (19,20). Nicotinic agonists has been shown to increase the release of soluble APP (10). If thiamine could be administered effectively in early AD, before significant losses of nicotinic receptors, it may have the potential to stimulate soluble APP release and reduce the generation of ß-amyloid.

Increased Expression of APOE 4 in Wernicke-Koraskoff Disease

The apolipoprotein epsilon 4 (APOE4) allele is associated with an dose-dependent increase in risk and earlier age-of-onset for AD (5). This allele occurs in both familial and sporadic cases (5). The disease-promoting effect of inheriting one or two APOE4 alleles seems to involve an enhanced aggregation, a decreased clearance of ß-amyloid peptides or both (reviewed in ref. 4). This allele has recently been associated with global intellectual deficits in Wernicke-Korasakoff Syndrome in a preliminary study (21). What is unclear is whether the presence of this allele would promote a genetic susceptibility to thiamine deficiency and altered APP processing or whether thiamine deficiency might alter allelic expression. As thiamine deficiency can alter protein (22) and DNA (23,24) synthesis, further research into the effect of thiamine deficiency on the expression of APOE4 alleles and amyloid metabolism may contribute to our understanding of the abnormalities in amyloid metabolism in AD.

Rodent Models of Thiamine Deficiency

Direct evidence of a role for thiamine in amyloid production comes from studies demonstrating a relationship between APP-like accumulation and selective cell damage following thiamine deficiency in pyrithiamine-treated rats (25,26) and mice (26,27). Although the APP-like accumulation in the rat brain (25) and mouse brain (27) was not associated with the deposition of dense highly organized amyloid structures of beta A4, the rodent is not a good model for such deposits (28). Non-human primates and other higher mammals appear to be the only animals to accumulate appreciable beta A4 deposits with aging (28).

Pyrithiamine-induced thiamine deficiency in mice has been shown to increase ß-amyloid 1-40 specific and amyloid precursor protein immunoreactivity where fiber cell degeneration was evident in mouse lenses (29). In AD, vascular amyloid is predominately Aß40 (30). Aß40 also occurs in AD plaques (4).

Conclusion

Although, to our knowledge, no study has yet demonstrated that thiamine treatment can correct abnormalities in amyloid metabolism in animal models, considerable evidence suggests that thiamine deficiency may play a role in amyloid pathogenesis. Moreover, based on knowledge of thiamine's role in metabolism the potential for correcting these abnormalities exists.

Putting the amyloid hypothesis of AD into perspective it must be remembered that plaque formation is not unique to AD, and can occur in non-demented aged (31). The differences that separate normal aging from AD relate to the extent and distribution of such lesions (31). In that light, amyloidogenesis is not likely to be the cause of AD but rather secondary to another factor.

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CHAPTER 11

NEW DIRECTIONS FOR RESEARCH

From this synthesis of literature in two research fields, nutrition and medicine, a new theory is proposed, ie., Alzheimer's Disease is a disease of thiamine deficiency. Countless more studies are needed. What are the questions?

Can biochemical evidence of thiamine deficiency be confirmed clinically in AD patients who are eating well? What measures are best used to determine this? Can correlations between these biomarkers and cognitive function be found?

If clinical evidence of thiamine deficiency is determined, what factors promote thiamine deficiency in this disease? Is the problem in gastrointestinal tract function or abnormalities in thiamine transport, excretion or utilization? How do risk factors for AD relate to thiamine status?

What is the potential for thiamine supplementation in AD? What forms of thiamine should be used, in what amounts, and at what stages of the disease process? Will supplementation prove beneficial even in patients with apparently adequate biochemical thiamine status? Can the disease process be slowed, stopped, reversed or prevented with thiamine supplementation?

The quest for answers must continue.

APPENDIX A

Medications Affecting Thiamine Status

Table 7.- Medications Affecting Thiamine Status

Type	Name	Mechanism	Reference
antacids	aluminum hydroxide magnesium hydroxide magnesium oxide aluminum phosphate calcium carbonate magnesium carbonate magnesium trisilicate sodium bicarbonate	inactivation of T in basic pH	1
antiarrythmic	digoxin	inhibit T uptake(cardiac cells)	2
		diarrhea	3
	quinidine	diarrhea	3
anticonvulsant	phenytoin	< T &TMP uptake, < TDP dephosphorylation to TMP, < TPP turnover time (rat brain)	4
	valproic acid	inactivates and inhibits alpha-KGDHC*	5
antidepressants (tricyclic)	amitriptyline imipramine doxepin amoxapine protriptyline lithium carbonate	> urinary excretion of B vitamins	6
antiinfective	furazolidone	> TPP effect (poultry)	7
		toxicity ameliorated by T (goat model)	8
		interferes with T utilization (goat model)	9

Table 7.- Medications Affecting Thiamine Status (cont'd)

Type	Name	Mechanism	Reference
antiinfective (cont'd)	metronidazole	T antagonist	10
	nitrofurazone	< ETKA, < TPP effect (chicken)	11
	penicillin	may > T absorption (rat)	12
	sulfonamides other than sulfasalazine	produces peripheral neuritis	1
			13
	sulfadiazine	thiamine sparing (<BMR)	
	sulfamerazine	thiamine sparing (<BMR)	13
	sulfasuxidine	thiamine sparing	12
antineoplastic fluoro-pyrimidines	5-fluorouracil	> cellular T metabolism	14
		thiamine deficiency	15
		may prevent T phosphorylation	16
		exaggerate existing thiamine deficiency	17
	doxifluridine	> cellular T metabolism	14
antipsychotic	haloperidol prochlorperazine chlorpromazine perphenazine trifluprom azine fluphenazine thioridazine thiothixene promazine trifluoperazine clozapine	inhibits PDHC*	18
barbituate	amobarbital barbital	< T absorption	1

Table 7.- Medications Affecting Thiamine Status (cont'd)

Type	Name	Mechanism	Reference
barbituate (cont'd)	butabarbital pentobarbital secobarbital	< T absorption	1
	vinbarbital		1
cardiotonic	digitalis alkaloids	may > T requirements	19
diuretic	furosemide	> urinary T loss	20
		"	21
		> TPP effect on ETKA	22
	chlormerodin meralluride mercaptomerin mercurophylline mersalyl	> urinary T loss	1
hormone	hydrocortisone	activate TPP degradation	23 (Review)
	insulin	inhibit TPP degradation	
hypotensive	reserpine	diarrhea	3
laxative	senna phenolphthalein	diarrhea	3
monoamine oxidase inhibitors	harmaline tranylcypromine deprenyl	< ETKA & > TPP effect (rabbit model)	24
proton channel blocking agent	omeprazole	T analog, inhibits TK and PDH	25
sedative	benzamide	>Km TPP	26
stimulant	metamphetamine	< TTP, TMP &TPP (rat brain)	27

Table 7.- Medications Affecting Thiamine Status (cont'd)

Type	Name	Mechanism	Reference
thiamine derivative	oxythiamin	thiamine antagonist	24
	oxythiamin diphosphate	inhibit TPP	28
	oxythiamine disulphide nicotinate	inhibit ETKA	29
	tetrahydroxythiamin diphosphate	inhibit TPP	28
	pyrithiamine	thiamine antagonist	24
	sulbutiamine	> TTP	30
Other drugs	alcohol	< T absorption	31
		"	32
		"	33
		< activity TPP synthesizing enzyme	34
		at high T plasma conc, > T transport rate	35
		contributes to poor dietary intake of T	36 (Review)
	butylphenol	> Km TPP	26
	contraceptives(oral) (unspecified)	> T requirement	37
	dichloroacetate	< ETKA (rat)	38

Table 7.- Medications Affecting Thiamine Status (cont'd)

Type	Name	Mechanism	Reference
Other drugs	nitroimidazole derivatives	antimetabolic effects	39

Codes: T=thiamine; TMP=thiamine monophosphate;TPP=thiamine pyrophosphate;TTP=thiamine triphosphate;TK=transketolase;ETKA=erythrocyte transketolase activity;PDH(C)=pyruvate dehydrogenase(complex);alpha-KGDHC=alpha-ketoglutarate dehydrogenase complex

*Drugs that affect PDHC and alpha-KGDHC alter thiamine biochemistry (TPP is a cofactor for PDHC and alpha-KGDHC activity)

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APPENDIX B

Disease and Conditions Affecting Thiamine Status

Table 8.- Diseases Affecting Thiamine Status

Disease	Effect on Thiamine Status	Reference
Alcoholism with or without liver disease	< serum, blood thiamine	1
Beriberi	thiamine deficiency	1
Cancer (some types)	< basal ETKA or > ETK-AC	2
Chronic Febrile Infections	< serum, blood thiamine	1
Diabetes	< blood transketolase	1
Gastrointestinal disease	malabsorption	3
Hepatic disease	> thiamine requirements	3
Hodgkin's Disease	>serum, blood thiamine	1
Hyperthyroidism	> thiamine requirements	3
Leukemia	> serum, blood thiamine	1
Pernicious Anemia	> blood transketolase	1
Polycythemia Vera	> serum, blood thiamine	1
Polyneuritis	< blood transketolase	1
Thiamine-Responsive Inborn Errors:		4
. Maple Syrup Urine Disease		1
. Megaloblastic anemia of unknown origin		1
. impaired pyruvate carboxylase		1
. impaired ketoacid dehydrogenase		1
. subacute necrotizing encephalopathy		
Uremic Neuropathy	< basal ETKA	2
Wernicke-Korsakoff Syndrome	thiamine deficiency	1

Code: ETKA= erythrocyte transketolase activity
ETK-AC = erythrocyte transketolase activity coefficient

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Table 9.- Conditions Affecting Thiamine Status

Condition	Effect on Thiamine Status	Reference
starvation		1
pregnancy	> thiamine requirements	2
B6 deficiency (rats)	< urinary and > fecal thiamine	3
B12 deficiency (rats)	< urinary thiamine	3
folate deficiency (rats)	thiamine depletion,<absorption	4,5
iron deficiency	> basal ETKA	6
magnesium deficiency (rats)		7
> carbohydrate intake	> thiamine requirements	8
fever	> thiamine requirements	8
muscular activity	> thiamine requirements	8

Code: ETKA=erythrocyte transketolase activity

Sources:

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