Published in final edited form as:
Mol Cell Neurosci. 2013 July ; 55: 17–25. doi:10.1016/j.mcn.2012.09.001.

Abnormal Thiamine-Dependent Processes in Alzheimer's Disease. Lessons from Diabetes

Gary E. Gibson[*,1], **Joseph A. Hirsch**[1], **Rosanna T. Cirio**[1], **Barry D. Jordan**[1], **Pasquale Fonzetti**[1], and **Jessica Elder**[2]

[1]Department of Neurology and Neuroscience, Burke Medical Research Institute, 785 Mamaroneck Avenue, White Plains, NY 10605

[2]Department of Epidemiology, Weill Cornell Medical College, Burke Medical Research Institute, 785 Mamaroneck Avenue, White Plains, NY 10605

Abstract

Reduced glucose metabolism is an invariant feature of Alzheimer's Disease (AD) and an outstanding biomarker of disease progression. Glucose metabolism may be an attractive therapeutic target, whether the decline initiates AD pathophysiology or is a critical component of a cascade. The cause of cerebral regional glucose hypometabolism remains unclear. Thiamine-dependent processes are critical in glucose metabolism and are diminished in brains of AD patients at autopsy. Further, the reductions in thiamine-dependent processes are highly correlated to the decline in clinical dementia rating scales. In animal models, thiamine deficiency exacerbates plaque formation, promotes phosphorylation of tau and impairs memory. In contrast, treatment of mouse models of AD with the thiamine derivative benfotiamine diminishes plaques, decreases phosphorylation of tau and reverses memory deficits. Diabetes predisposes to AD, which suggests they may share some common mechanisms. Benfotiamine diminishes peripheral neuropathy in diabetic humans and animals. In diabetes, benfotiamine induces key thiamine-dependent enzymes of the pentose shunt to reduce accumulation of toxic metabolites including advanced glycation end products (AGE). Related mechanisms may lead to reversal of plaque formation by benfotiamine in animals. If so, the use of benfotiamine could provide a safe intervention to reverse biological and clinical processes of AD progression.

Keywords

Thiamine; Alzheimer's disease; diabetes; mitochondria; pentose shunt; transketolase

Introduction

Alzheimer's Disease (AD) affects approximately 5.4 million Americans and is a major public health problem. One in eight individuals over the age of 65 (13%) and nearly half of those over the age of 85 (43%) have AD. Between 2000 and 2008 the frequency of deaths due to AD increased 66%, whereas those from stroke (−20%), prostate cancer (−8%), breast cancer (−3%), heart disease (−13%) and HIV (−29%) actually decreased. The cost of care is

*Corresponding author. Phone 914-597-2291, ggibson@med.cornell.edu.

projected to increase from $200 billion dollars in 2012 to $1.1 trillion by 2050 (data from the Alzheimer Association; http://www.alz.org/alzheimers_disease_facts_and_figures.asp).

AD is defined by a decline in cognition and pathological features including plaques and tangles. The primary protein in plaques is amyloid-β-peptide. Tangles are composed of hyperphosphorylated tau protein. Although these pathologies are the defining feature of the disease, many other factors change and may initiate the pathology including altered glucose metabolism, which is discussed in detail below. Multiple therapeutic strategies are being tested but no disease modifying therapies have been developed. The majority of treatments have been directed at modifying plaques by decreasing deposition or enhancing removal (Rafii and Aisen, 2009). Treatments are also being tested to modify tangle deposition (Citron, 2010). Multiple treatments have also been proposed to treat the abnormalities in glucose metabolism (Dumont et al., 2010; Manczak et al., 2010). The strategy described below is novel.

Reduced glucose metabolism is an invariant feature of Alzheimer's disease (AD) regardless of genotype

Fluoro-DeoxyGlucose-PET (FDG-PET) studies in patients with AD show decreased glucose uptake bilaterally in posterior cingulate, precuneus, parietotemporal and frontal cortex. Greater decreases in FDG uptake correlate with greater cognitive impairment along the continuum from normal cognitive status to mild cognitive impairment (MCI) to AD dementia (Langbaum et al., 2009). A great advantage in patients with a disease causing mutation is that the temporal response of the changes can be followed. In patients that are genetically inclined to develop AD, changes in brain glucose metabolism occur decades before the development of symptoms (Reiman et al., 2004). There are no reports of normal glucose metabolism in brains of AD patients.

Increases in several markers of oxidative stress also indicate altered metabolism in patients with AD. In autopsy brains, markers of oxidative stress such as acrolein are more pervasive than plaques or tangles (Calingasan et al., 1999). Advanced glycation end products (AGE) occur in 75-95% of pyramidal neurons, which far exceeds the percentage of tau positive neurons (Munch et al., 2002). Markers of oxidative stress occur in peripheral cells formation in even mildly cognitively impaired patients (Torres et al., 2011). In animal models of plaque formation, markers of oxidative stress in brain and urine increase before plaques occur in brain (Praticò et al., 2001). Despite major advances in early diagnosis, neuroimaging, and biomarker research, no disease-modifying therapies are currently available. A possible cause for this failure is that alternative targets are required. Thus, understanding the changes in glucose metabolism may provide insight into new therapeutic targets.

Reduced glucose metabolism is the best predictor of progression from "normal" or mild cognitive impairment to AD

A large, multicenter, longitudinal neuroimaging study [(Alzheimer Disease Neuroimaging Initiative (ADNI)] was launched in 2004 by the National Institute on Aging, the FDA, private pharmaceutical companies, and nonprofit organizations to better understand the initiation and progression of AD. The ADNI study includes 819 adult subjects, 55 to 90 years old that are either healthy, suffer from mild cognitive impairment or mild AD. Participants receive baseline and periodic physical and neurological examinations and standardized neuropsychological assessments, and provide biological samples (blood, urine, CSF) throughout the study. Imaging, including F^{18} -fluorodeoxyglucose (FDG) positron emission tomography (PET), is performed at baseline and at regular intervals thereafter. The

conclusion of these studies is that the best predictor of developing and of progressing from mild cognitive impairment (MCI) to AD is brain glucose utilization (Jack Jr et al., 2010).

The mechanism for the decline in glucose with AD is unknown

In spite of the tight linkage of glucose metabolism to brain function and to the decline in AD, only a very limited number of studies have tried to understand why it is diminished. In related efforts, many experiments to enhance mitogenesis (Burchell et al., 2010) or diminish oxidative stress in the brain (Dumont and Beal, 2011; Eckert et al., 2011) have been completed, but none of the therapies have translated to the clinic. The focus of this review is the reduction in thiamine-dependent processes in AD brains and how they could account for the decline in glucose metabolism and/or the pathology in AD. The resemblances of the changes in AD to thiamine (vitamin B1) reversible steps in diabetes suggest that thiamine may also be beneficial for AD.

Thiamine (vitamin B1)-dependent processes occupy critical steps in glucose metabolism (Figure 1)

Normal brain function depends on a continuous supply of glucose. Brain glucose metabolism depends on three thiamine-dependent enzymes (Figure 1): transketolase (TK), the pyruvate dehydrogenase complex (PDHC) and the α-ketoglutarate dehydrogenase complex (KGDHC). TK is the rate-controlling step of the non-oxidative branch of the pentose phosphate pathway (NOPPP), is central to the oxidative branch, and is critical in the interchange of metabolites between glycolysis and the pentose shunt (Kauffman, 1972; Novello and McLean, 1968). PDHC is the entry point of carbon into the tricarboxylic acid (TCA) cycle. KGDHC is arguably the rate-controlling step of the TCA cycle under normal conditions (i.e., it has a high flux control coefficient)(Gibson and Blass, 1976). Thus, thiamine-dependent processes regulate essential aspects of brain glucose metabolism that are critical to normal brain function.

Glycolysis is important for providing some reducing equivalents, pyruvate for the TCA cycle and precursors for numerous amino acids and neurotransmitters. Oxidant-induced modification in glyceraldehyde-3-phosphate dehydrogenase (GAPDH) promotes accumulation of toxic metabolites that may precipitate pathological changes in the other pathways in both AD and diabetes (see Figure 2). Reductions in the GAPDH reaction by oxidant stress leads to accumulation of fructose-6-phosphate and glyceraldehyde-3 phosphate, which are precursors of toxic metabolites.

An increase in fructose-6 phosphate leads to leads to increased glucosamine, uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) and N-acetylglucosamine:

↑ fructose-6-P→ ↑ glucosamine 6-phosphate → UDP-GlcNAC→ N-acetylglucosamine
Several important processes require UDP-GlcNAC such as proteoglycan synthesis and the formation of *O*-linked glycoproteins. The glycosylation of the proteins modifies their actions. Inhibition of the rate-limiting enzyme in the conversion of glucose to glucosamine blocks hyperglycaemia-induced increases in the transcription of TGF-α, TGF-β1 and PAI-1 (Du et al., 2001). This pathway is also important role in hyperglycemia-induced and fat-induced insulin resistance (Brownlee, 2001). Virtually every RNA polymerase II transcription factor has *O*- acetylglucosaminylated sites. The reciprocal modification by *O*-acetylglucosaminylation and phosphorylation of transcription factors other than Sp1 may function as a more generalized mechanism for regulating glucose-responsive gene transcription (Brownlee, 2001). This reciprocal interaction may also be critical for the phosphorylation of tau, which is critical to tangle formation in AD (Liu et al., 2004). A reduction in the *O*-acetylglucosaminylation leads to increased phosphorylation and tangle

formation. Other examples include the inhibition of eNOS activity by hyperglycaemia-induced *O*-acetylglucosaminylation at the Akt site of the eNOS protein (Du et al., 2001). Thus, the O-linked glycoproteins may result in numerous changes in gene expression and protein function. Abnormally regulated *O*-acetylglucosaminylation has been found in diabetes and Alzheimer disease (Wang et al., 2007).

An increase in glyceraldehyde-3-phosphate enhances diacylglycerol pathway that leads to the increased formation of methyglyoxal which leads to increased advance glycation endproducts (AGE), which play an important role in the development of chronic disease including diabetes (Brownlee et al., 1986; Thorpe and Baynes, 1996) (Figure 2). AGEs are a heterogeneous and complex group of biochemical modifications, which play an important role in the development of chronic disease including diabetes (Brownlee et al., 1986). AGE are markers of carbonyl stress, which accumulate due to an increase level of reactive dicarbonyl compounds (Thorpe and Baynes, 1996). Methylglyoxal and glyoxal are the major carbonyl species responsible for AGE (Krautwald and Munch, 2010). AGEs damage cells by a variety of processes including neurotoxicity, oxidative stress and apoptosis (Bettendorff et al., 1990; Loske et al., 1998). AGEs may elicit their effects via receptors and binding proteins which are broadly thought to be either inflammatory (e.g. RAGE) or “clearance” receptors (such as AGE-R1, AGE-R3, CD36, Scr-II) (Bierhaus et al., 1998; Sourris et al., 2009). Intracellular proteins modified by AGEs have altered function. For example, extracellular matrix components modified by AGE precursors interact abnormally with other matrix components and with the receptors for matrix proteins (integrins) on cells. Plasma proteins modified by AGE precursors bind to AGE receptors on endothelial cells, mesangial cells and macrophages, inducing receptor-mediated production of reactive oxygen species. This AGE receptor ligation activates the pleiotropic transcription factor NF-kB, causing pathological changes in gene expression (Brownlee, 2001). Thus, ameliorating AGE is an attractive therapeutic approach.

The response of AGEs to thiamine availability has been demonstrated *in vivo*. Thiamine has an essential role in sustaining low levels of cellular defense against the accumulation of AGE related to glucose metabolism (Depeint et al., 2007). Even marginal thiamine deficiency (TD) increases plasma AGE (Lonsdale, 2006; Shangari et al., 2003). The combination of dietary TD and other sources of dietary oxidative stress synergistically increase AGE (Shangari et al., 2005). Marginal TD increases oxidative stress in a dose dependent manner that can be assessed by increased plasma and tissue concentration of AGE (Depeint et al., 2007).

Pentose shunt

The role of the pentose phosphate shunt in brain is controversial. The role of the transketolase dependent part of the shunt non-oxidative pentose phosphate shunt has received minimal attention in brain. The shunt is critical for production of riboses for DNA and RNA synthesis, removal of toxic metabolites and for maintaining NADP(H) (Figure 3). Recent studies show the pentose shunt in brain is much more active than previously thought; it has been suggested that the shunt consumes the majority of glucose in neurons (Bolanos and Almeida, 2010; Bolanos et al., 2010). The results also suggest that neuronal consumption of glucose by the pentose phosphate shunt to maintain their antioxidant status may take priority over the use of glucose to fulfill their bio-energetic requirements, which can be met by other sources. An alternative explanation is that these data are merely an artifact of cultured neurons severely crippled by the extraction procedure and grown in un-naturally glucose-rich environment under un-physiological hyper-oxygenation that causes severe oxidative stress exhausting the natural antioxidant defense capacity of these neurons. *In vivo* data and/or alternative strategies are required to distinguish these possibilities. Furthermore, the shunt is much more active in neurons than in astrocytes. Increasing

evidence indicates that neurons can use lactate generated by astrocytes to produce energy (Herrero-Mendez et al., 2009). This provides an explanation for greater sensitivity of neuron than astrocytes to thiamine deficiency (Park et al., 2000).

The pentose shunt is composed of multiple pathways that are flexible and can vary with the demands for ribose and NADPH to maintain antioxidant capacity. The pentose shunt is linked to glycolysis at multiple steps and many of the steps are reversible. This maximizes the ability to produce energy, riboses or reducing equivalents (i.e., NADPH). Thus, it can either provide the glycolytic metabolites fructose 6 phosphate (7) and glyceraldehyde 3 phosphate (5) or it can be activated to use fructose 6 phosphate (7) and glyceraldehyde 3 phosphate (5) to make riboses. The latter is important to allow it to remove toxic metabolites that result from impairment of glycolysis.A simplified version of the predominant pathways within the pentose shunt are shown in Figure 3. The thiamine-dependent enzyme transketolase (TK) is critical at two steps in these interacting pathways. The oxidative pathway is shown in the shaded area. The numbers in the cartoon refer to metabolites of the pentose shunt. The same number in multiple places indicates the compound is involved in multiple sites and thus serves as a link between glycolysis and the pentose shunt (#5 glyceraldehyde-3-phosphate is a good example).

Glucose-6-phosphate (1) is oxidatively decarboxylated to yield ribulose-5-phosphate (2) which is converted to ribose-5-phosphate (3) and xylulose-5-phosphate (4). TK catalyses the reversible conversion of ribose-5-phosphate (3) and xylulose-5-phosphate (4) into glyceraldehyde-3-phosphate (5) and sedoheptulose-7-phosphate (6). These latter two react to form fructose-6-phosphate (7) and erythrose-4-phosphate (8).Transketolase catalyzes the conversion of xylulose-5-phosphate (4) and erythrose-4-phosphate (8) to glyceraldehyde-3-phosphate (5) and fructose-6-phosphate (7).

Many of the reactions are reversible so that increasing TK with thiamine supplements enhances the conversion of fructose-6-phosphate (7) and glyceraldehyde-3-phosphate (5) to riboses. Since the *in vivo* concentration of transketolase metabolites is at least one order of magnitude lower than the Km values, the net flux and direction of the transketolase reaction is determined by substrate concentration (Schenk et al., 1998). The activation of the pathway in this direction can reduce the concentration of fructose-6-phosphate (#7) and glyceraldehyde-3-phosphate (#5). As described previously, inhibition of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) by multiple oxidants leads to accumulation of toxic metabolites. These compounds accumulate in diabetes. Supplements with thiamine or its derivative benfotiamine activate transketolase, reduce the concentrations of these compounds and decrease peripheral neuropathy.

TCA cycle

Two other thiamine-dependent processes are closely linked to the TCA cycle, which provides the majority of reducing equivalents to the electron transport chain. In addition, the TCA cycle produces guanosine triphosphate (GTP) and provides precursors for multiple amino acids and neurotransmitters. For example, both PDHC and KGDHC are closely linked to acetylcholine synthesis (Gibson and Blass, 1976; Gibson et al., 1975). Even mild impairment of either of these thiamine-dependent enzyme activities reduces acetylcholine synthesis even though only a small part of total carbons enters acetylcholine. Heme synthesis also depends on the TCA cycle (Atamna and Kumar, 2010). In addition, under reducing conditions, PDHC and KGDHC can be the primary sources of H_2O_2 (Starkov et al., 2004; Tretter and Adam-Vizi, 2004).

Thiamine (vitamin B1)-dependent processes are altered in AD

Measurements in autopsy brains suggest that diminished activities of thiamine-dependent enzymes underlie the glucose deficits. We and others have demonstrated an AD-related reduction in the thiamine-dependent processes including transketolase, PDHC and KGDHC (Bubber et al., 2005; Butterworth and Besnard, 1990; Gibson et al., 2000; Gibson et al., 1988). We propose that these reductions may underlie the decline in glucose metabolism. The reductions in the activities of KGDHC and PDHC are highly correlated with the clinical dementia rating score (Morris, 1993) in AD patients prior to succumbing to the disease. The correlation is 0.77 compared to a correlation of 0.2 for plaques and tangles. Moreover, thiamine deficiency is known to lead to severe memory deficits in both animals and humans (Bubber et al., 2005; Butterworth and Besnard, 1990; Gibson et al., 2000; Gibson et al., 1988).

Although the decline in KGDHC activity occurs in both genetic and non-genetic forms of AD, the underlying basis for the reduction may vary. For example, in patients bearing the APP670/671 mutation the protein levels of two components of the KGDHC complex decline, whereas in non-genetic forms the protein levels do not vary (Gibson et al., 1998). These changes can be mimicked by selective actions of nitric oxide and peroxynitrite (Gibson et al., 1999). Inactivation of KGDHC by peroxynitrite diminishes the immunoreactivity of the same KGDHC subunits, whereas nitric oxide diminishes activity but does not alter protein levels (Park et al., 1999).

Measurements in peripheral tissues suggest thiamine-dependent processes may be altered specifically in AD (Gibson et al., 1988). Plasma thiamine levels are diminished in AD patients and not in Parkinson patients (Gold et al., 1998). The thiamine pyrophosphate (TPP) effect on transketolase, a measure of thiamine deficiency, is also significantly higher in red blood cells (RBC) from AD patients compared with controls (Gibson et al., 1988).

Studies in animal models suggest that abnormal thiamine-dependent processes underlie pathological changes in AD

Animal models suggest that thiamine has a critical role in the pathology of AD. Thiamine deficiency (TD) is a model of the mild impairment of oxidative metabolism that accompanies AD. TD induces many markers of oxidative stress in neurons that resemble those in AD including hydroxynonenal and protein nitration. TD depresses brain glucose utilization (Hakim and Pappius, 1983). Administering thiamine to TD rats improves their ability to use glucose (Gibson et al., 1984).TD induces memory loss (Witt and Goldman-Rakic, 1983). TD in plaque-competent mice exacerbates plaque formation and increases tau phosphorylation (i.e., promotes AD pathology) (Karuppagounder et al., 2009; Zhang et al., 2011; Zhao et al., 2011). TD also produces a cholinergic deficit (Gibson et al., 1982). A cholinergic deficit accompanies AD and is the reason that the acetylcholinesterase inhibitor donepezil is partially effective in AD..The alterations in glucose metabolism due to TD also lead to excess glutamate release (Hazell et al., 1993). Unregulated or excessive glutamate receptor activation, may also have a role in the pathogenesis of Alzheimer’s disease (AD). Over stimulating various glutamate receptors leads to excitotoxicity and neuronal cell death. Excess glutamate release is also thought to accompany AD and is the reason the glutamate receptor blocker memanitine is partially effective in AD (Reisberg et al., 2003) .

The memory loss in thiamine deficient humans (i.e., Wernicke patients) has been compared to that in Alzheimer’s disease patients. The intercorrelation of eight executive function or “frontal’ tests in 32 patients with Korsakoff s syndrome and Alzheimer’s disease was investigated. The defective retrieval of retrograde memories was correlated with frontal dysfunction in both patient groups. A stepwise regression analysis based on three frontal

tests could account for 64% of the variability in retrograde memory performance within the total patient group, 68.5% in the Korsakoff group and 57% in the Alzheimer group. It is concluded that frontal dysfunction produces a disorganization of retrieval processes which contributes to the temporally-extensive retrograde amnesia of these two disorders (Kopelman, 1991).

AD is associated with abnormal calcium regulation (Gibson and Peterson, 1987) and this can be caused by reductions in thiamine-dependent processes (Gibson et al., 2011). Increased endoplasmic reticulum calcium store occurs in fibroblasts from AD patients (Ito et al., 1994) and in fibroblasts and neurons from transgenic mice bearing AD causing mutations (Leissring et al., 2000) (Figure 4).Furthermore, mutations in presenilin that lead to AD cause this same increase in endoplasmic reticulum calcium stores. However, the cause of the change in the vast majority of AD cases in unknown. Reductions in the thiamine-dependent enzyme KGDHC can also lead to increases in ER calcium. If KGDHC is diminished by approximately one half by either adenovirus or by using neurons from transgenic mice that are heterozygous for KGDHC, calcium is also increased in the ER (Shi and Gibson, 2011) (See Figure 4).

Neuronal death due to thiamine deficiency has many parallels to neuronal death in AD (Ke and Gibson, 2004). TD induces neuronal death in specific brain regions. Endothelial cells are particularly sensitive. The neuronal death is preceded by endothelial cell change including an induction eNOS and ICAM-1 and by microglial activation. As in AD, neurons die, but microglia, endothelial cells and astrocytes appear to be activated. Studies in transgenic mice show that blocking the endothelial cell response can be protective (Ke and Gibson, 2004). The brains of thiamine deficient mice also have increased ROS damage in their brains including that caused by free radicals derived from nitric oxide (Ke and Gibson, 2004).

Abnormal neurogenesis is common to thiamine deficiency and diabetes. Diminished neurogenesis is an early event in the mouse plaque models, and the decline can be feasibly linked to the memory deficits (Demars et al., 2010) (Rodriguez et al., 2008). Reduced neurogenesis in the hippocampal progenitor zone is an early event in TD (Hata et al., 1987) and in mice with a reduction of thiamine-dependent enzymes by genetic manipulation (Calingasan et al., 2008). The reduction in neurogenesis in TD mice is linked to a reduction in transketolase (Meyer et al., 1985). Thiamine partially reverses the inflammation-associated impairment of neurogenesis *in vitro* and in irradiated mice *in vivo* (Volobouéva et al., 2010). In diabetes, the level of thiamine correlates to the number of endothelial cell progenitor cells (Wong et al., 2008).

These observations suggest that thiamine based therapies may be effective

Thiamine normally enters the brain through low capacity transporters. Thiamine is then phosphorylated to thiamine disphosphate ester (frequently referred to as thiamine pyrophosphate, TPP), which is the form of thiamine that is required for thiamine dependent enzymes.

Thiamine→Thiamine Monophosphate (TMP)→Thiamine Diphosphate (TDP or TPP) In addition, non-cofactor roles of the triphosphorylated derivatives thiamin triphosphate (ThTP) and adenosine thiamin triphosphate (AThTP) may play a role in metabolic regulation and may contribute to the pathology of thiamine deficiency-induced brain lesions (Bettendorff, 2012).

Thiamine is a water soluble compound that does not penetrate membranes very well. This decreases its absorption from the gut and its movement into cells and across the blood brain

barrier. Thus, thiamine derivatives that are able to increase cell thiamine more efficiently than thiamine have been developed (See Figure 5). Benfotiamine is perhaps the best studied of these derivatives. Benfotiamine (S-benzoylthiamine-O-monophosphate) is the most potent of the allithiamines, a unique class of thiamin-derived compounds present in trace quantities in roasted crushed garlic and other vegetables from the Allium genus (such as onions, shallots, and leeks). Benfotiamine contains an open thiazole ring that is closed on reduction within the cell. Benfotiamine enters cells more easily than thiamine and maintains the active form of thiamine (TPP) for longer periods. Thiamine absorption from benfotiamine is about five times as great as from conventional thiamine supplements (Loew, 1996). Peripheral cells take in five- to twenty-five-fold as much thiamine in the form of allithiamines as they do of an equal amount of regular thiamine (benfotiamine.org).

Studies in humans show that benfotiamine increases blood thiamine and thiamine diphosphate much more than equivalent dosages of thiamine (Frank et al., 2000; Loew, 1996). Benfotiamine only penetrates the cells after de-phosphorylation by intestinal alkaline phosphatases. It then enters the bloodstream as S-benzoylthiamine that is converted to thiamine in erythrocytes and in the liver. Following oral administration of 250 mg benfotiamine in humans, thiamine peaks within one hour in blood, and returns to normal by 25 hours. However, thiamine diphosphate peaks in blood at about 5 hours at about 2 times control value and remains at that level for 25 hours (Ziems et al., 2000). Several groups have shown in mice, similar to humans, that administration of benfotiamine rapidly increases thiamine in liver and blood to reach a maximum in about one or two hours, respectively. During this time, brain thiamine does not increase. The reported effects after longer-term administration (10-14 days) vary. In one report, thiamine does not increase in brain (Volvert et al., 2008), whereas in the other (Pan et al., 2010b) brain thiamine is elevated. Neither show increases in the thiamine esters. One study showed a 90% increase in thiamine diphosphate levels in brain of rats that received benfotiamine in their diet for 6 months followed by 6 months of thiamine (Netzel et al., 2000). In the paper in which plaque levels were diminished (see below) (Pan et al., 2010b), the treatment was over an eight-week period. However, thiamine was only measured one hour after a single dosage or after a 10-day trial. In both, benfotiamine increased the levels of thiamine but not TMP or TDP in brain, whereas the levels of all were increased in blood. As with all the studies, the increase in blood and liver was much larger than in brain (Pan et al., 2010b). Our unpublished studies in mice demonstrate that six months of benfotiamine feeding increases blood thiamine by 40 fold and brain thiamine by over 50% (Dumont et al.). What is not known is if the brain is thiamine deficient, how the different thiamine derivatives will replace the missing thiamine.

Sulbutiamine is a lipophilic derivative of thiamine that more readily crosses membranes than thiamine. Chronic administration of sulbutiamine improves long-term memory formation in mice (Micheau et al., 1985). Chronic treatment with sulbutiamine improves memory in an object recognition task and reduces some amnesic effects of dizocilpine in a spatial delayed-non-match-to-sample task (Bizot et al., 2005).

Fursultiamine has not been studied as extensively as sulbutiamine of benfotiamine. Studies show that it increases brain thiamine as effectively as benfotiamine (Pan et al., 2010b).

Measuring thiamine levels in brain may not provide an adequate measure of the functional consequences of thiamine supplements. For example, one group claims benfotiamine increases brain thiamine (Pan et al., 2010a), whereas others claim it does not (Volvert et al., 2008). Another report found slight increases after six months (Netzel et al., 2000). Others report that both benfotiamine and fursultiamine increase brain thiamine, but not thiamine esters, and only benfotiamine diminishes plaques (Pan et al., 2010a). Measures of the functional consequences of thiamine supplementation provide an effective screen for

thiamine-mimetics that may correct a functional thiamine deficiency in brain. The reversal of the decline in the activities of KGDHC and transketolase following TD provides a measure of the functional consequences of thiamine (Gibson et al., 1984). The various thiamine derivatives have not been tested in this manner. A limitation of any method is that providing thiamine (or a derivative) to thiamine sufficient animal models may not provide an adequate method to test for effects in functional deficient in patients. Further, tests done by adding thiamine or thiamine derivatives to thiamine deficient animals do not provide the possibility of testing for prolonged times since the reversal is rapid.

Thiamine supplements and AD pathology

The studies described above suggest that supplementation with thiamine or thiamine derivatives may be able to reverse AD pathological processes. Remarkably, supplements with thiamine derivatives decrease plaque formation and improve memory, even in mice that are genetically engineered to make plaques. Specifically, recent studies in mice show supplementing with the thiamine derivative benfotiamine diminish plaque formation and improve memory (Pan et al., 2010b). Another thiamine derivative, fursultiamine, is not effective, and our unpublished studies show that thiamine does not diminish plaque formation. The precise basis for this selectivity between thiamine and different thiamine derivatives is a matter of speculation, and is discussed in more detail later in the review. The inability of thiamine and fursultiamine to reverse plaques may be related to their ability to enhance thiamine dependent processes within the brain.

Diabetes, AD and thiamine

Diabetes predisposes to AD (Arvanitakis et al., 2004) and is also accompanied by profound alterations in glucose metabolism including a reduction in brain glucose metabolism. Insulin levels and insulin activity in the central nervous system are reduced in AD. Reduced levels of insulin and of insulin activity may contribute to a number of pathological processes that characterize AD. Indeed, recent studies examined the effects of intranasal insulin administration on cognition, function, cerebral glucose metabolism, and cerebrospinal fluid biomarkers in adults with MCI or AD. Insulin improved delayed memory, preserved caregiver-rated functional ability, preserved general cognition as assessed by the ADAS-cog score and functional abilities as assessed by the ADCS-ADL scale. Insulin treatment minimized the progression of deficits in glucose metabolism (Craft et al., 2012).

Considerable evidence suggests a role of thiamine-dependent processes in diabetes so that these studies can inform us about the role of these processes in AD. Diabetes, AD and thiamine deficiency share some pathological markers including AGE and their receptor RAGE. Diabetic peripheral neuropathy in both human and animal models of diabetes is responsive to thiamine or to the thiamine-mimetics that increase tissue thiamine better than thiamine. Induction of transketolase by thiamine is particularly important for the efficacy of thiamine's efficacy in diabetes (Hammes et al., 2003).

Thiamine diminishes adverse event related to diabetes

Hyperglycaemia increases the formation of AGE. Thiamine, especially the thiamine derivative benfotiamine, reduces hyperglycemia induced AGE in endothelial cells (La Selva et al., 1996; Stracke et al., 2001; Thornalley et al., 2001). Benfotiamine can also diminish cerebral oxidative stress associated with diabetes (Reggiani et al., 1984). In addition to the many small studies that have been done, a multi- center trial showed positive results. These studies also carefully document the safety of administering benfotiamine (Stracke et al., 2008). Strong evidence suggests that benfotiamine or thiamine does this by inducing transketolase. The data suggests that activation of transketolase reduces the AGE by activation of non-oxidative branch of the pentose phosphate shunt (Hammes et al., 2003;

Stracke et al., 2008). Growing cells in high glucose is one model of diabetes. Culturing cells with high glucose does not significantly depress transketolase, but the addition of thiamine or its derivatives to stressed cells increases transketolase and diminishes the toxic metabolites. If the increase in transketolase is blocked by using antisense oligonucleotides, thiamine is no longer neuro-protective. Thiamine does not increase transketolase in controls (Hammes et al., 2003). Successful treatment of diabetic peripheral neuropathy by activation of transketolase with thiamine-mimetics suggests a similar strategy may work in AD.

AGEs appear to be important components in the pathology of AD and diabetes. In AD brains, intracellular accumulation of AGE occurs in 75-95% of pyramidal neurons, which far exceeds the percentage of tau positive neurons. They also occur by the age of 35-45 years (Munch et al., 2002). In addition, AGEs may represent a driving force in acceleration of amyloid deposition and plaque formation (Loske et al., 2000). High levels of AGEs occur in neurofibrillary tangles (Jono et al., 2002) and CSF (Ahmed et al., 2005). The Mini-Mental State Examination (MMSE) score correlates negatively with oxidant-induced protein modification (Ahmed et al., 2005). Thus, the evidence for AGE is overwhelming for AD. These results raise the question of whether the AGEs in AD are due to a functional TD and/or if increasing thiamine availability in brain could overcome these deficits.

Thiamine may also be protective in AD and diabetes by acting at a transcriptional level. In bacterial systems, thiamine is known to regulate the transcription of the thiamine biosynthetic enzymes through well characterized riboswitches (Sudarsan et al., 2005). Such riboswitches have not been demonstrated in mammals, which do not make thiamine. In mammalian systems, indirect experiments with blood cells and brain suggest that thiamine can regulate the transcription of transketolase. Thiamine deficiency decreases steady-state transketolase and PDHC, but not KGDHC mRNA levels in three human cell types (Pekovich et al., 1998). The actions of the thiamine-mimetics suggest that actions not related to traditional thiamine-dependent enzymes may be important. Several metabolic proteins are increased following thiamine administration (e.g., glucose transporter2), but it is unknown if this is a transcriptional effect.

Implications of these findings for the treatment of AD are summarized in Figure 6

Decreased thiamine-dependent enzymes, diminished glucose metabolism, decreased metabolism and increased plaques and tangles all occur in brains from AD patients. However, the sequence of events is not certain. The data are consistent with the suggestion that the AD related decline in glucose utilization leads to the symptoms and is caused by a reduction in thiamine (vitamin B1) dependent enzymes in the brain. If this interpretation is correct, the inverse (i.e., increasing thiamine-dependent enzymes) could be beneficial.

Although thiamine-dependent processes appear to be appropriate therapeutic targets, the few previous trials have been minimally effective. One cause of the failure was that all were greatly under-powered so neither positive nor negative results are credible. The studies with thiamine were for short time periods and had small numbers of patients (i.e., they were poorly powered). The first was a double-blind, placebo-controlled crossover study, in which each patient received either placebo or thiamine followed by 3 months of the alternate treatment. Efficacy measures were the Mini-Mental State Examination (MMSE), and the caregiver-scored Haycox behavioral scale. While mean MMSE scores during treatment with thiamine were significantly better scores on the behavioral rating scales than during the placebo period, no significant difference was observed in (Blass et al., 1988). A one year trial of thiamine failed to replicate the changes described in this study (Nolan et al., 1991). Another study examined the effects of 3 to 8 g/day thiamine administered orally. The results suggest that thiamine at these pharmacologic dosages may have a mild beneficial effect in dementia of Alzheimer's type. (Meador et al., 1993).

Clinical studies have also been performed with thiamine derivatives. Fursultiamine had a mild beneficial effect in patients with Alzheimer's disease in a 12-week open trial. The improvement could be observed on emotional and other mental symptoms as well on intellectual function. Mildly impaired subjects showed cognitive improvement as shown by Hasegawa Dementia Scale and the Mini-Mental Status Exam (MMSE)(Mimori et al., 1996). As discussed above, in mouse models of plaque formation, fursultimaine did not clear the plaque even though benfotimine did.

Sulbutiamine potentiates cholinergic and glutamatergic transmissions, mainly in the hippocampus and prefrontal cortex. A multicenter, randomized and double-blind trial evaluated the effects of the association of sulbutiamine to a cholinesterase inhibitor on cognitive functions in patients with AD at an early stage (episodic memory, working memory, executive functions, attention). Patients first had anti-cholinesterase or sulbutiamine for three months. During this period, attention improved in both groups. During the three following months, one group received a placebo with the anticholinersterase and one group received sulbutiamine with the anticholinersterase. Compared to entry results, episodic memory decreased in the group with anticholinersterase but improved in the group with sulbutiamine plus anticholinersterase. At the same time the improvement of attention persisted in both groups. Activities of daily living also improved in the sulbutiamine group (Ollat H et al., 2007).

Thus, thiamine-dependent processes are abnormal in AD and diabetes. Thiamine based therapies have been successful in treating peripheral neuropathies in diabetes. The limited trials in AD have provided positive hints, but have generally been underpowered. Methods should be established for increasing functional thiamine in the brain and should then be tested in AD.

Acknowledgments

Supported by NIH PPG AG14930

Abbreviations

AD	Alzheimer's Disease
ADNI	Alzheimer Disease Neuroimaging Initiative
AGE	advanced glycation end products
ER	Endoplasmic reticulum
FDG-PET	Fluoro-DeoxyGlucose-Positron Emission Tomography
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
KGDHC	α-ketoglutarate dehydrogenase complex
ICDHC	isocitrate dehydrogenase complex)
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination
MDH	malate dehydrogenase
NOPPP	non-oxidative branch of the pentose phosphate pathway
PDHC	pyruvate dehydrogenase complex
RAGE	Receptor for advanced glycation endproducts

RBC	red blood cells
SDH	succinate dehydrogenase
TCA	tricarboxylic acid
TD	thiamine deficiency
TK	transketolase
TMP	Thiamine Monophosphate
TDP	Thiamine Diphosphate or TPP
TPP	Thiamine pyrophosphate
TTFD	Fursultiamine
UDP	GlcNAc uridine diphosphate N-acetylglucosamine

References

Ahmed N, Ahmed U, Thornalley PJ, Hager K, Fleischer G, Munch G. Protein glycation, oxidation and nitration adduct residues and free adducts of cerebrospinal fluid in Alzheimer's disease and link to cognitive impairment. J Neurochem. 2005; 92:255–263. [PubMed: 15663474]

Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. Arch Neurol. 2004; 61:661–666. [PubMed: 15148141]

Atamna H, Kumar R. Protective role of methylene blue in Alzheimer's disease via mitochondria and cytochrome c oxidase. J Alzheimers Dis. 2010; 20(Suppl 2):S439–452. benfotiamine.org. [PubMed: 20463399]

Bettendorff, L. Thiamine. In: Erdman, JW.; MacDonald, IA.; Zeisel, SH., editors. Present Knowledge in Nutrition. Wiley-Blackwell; 2012.

Bettendorff L, Weekers L, Wins P, Schoffeniels E. Injection of sulbutiamine induces an increase in thiamine triphosphate in rat tissues. Biochem Pharmacol. 1990; 40:2557–2560. [PubMed: 2268373]

Bierhaus A, Hofmann MA, Ziegler R, Nawroth PP. AGEs and their interaction with AGE-receptors in vascular disease and diabetes mellitus. I. The AGE concept. Cardiovasc Res. 1998; 37:586–600. [PubMed: 9659442]

Bizot J-C, Herpin A, Pothion S, Pirot S, Trovero F, Ollat H. Chronic treatment with sulbutiamine improves memory in an object recognition task and reduces some amnesic effects of dizocilpine in a spatial delayed-non-match-to-sample task. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2005; 29:928–935. [PubMed: 15951087]

Blass JP, Gleason P, Brush D, DiPonte P, Thaler H. Thiamine and Alzheimer's disease. A pilot study. Arch Neurol. 1988; 45:833–835. [PubMed: 2969232]

Bolanos JP, Almeida A. The pentose-phosphate pathway in neuronal survival against nitrosative stress. IUBMB Life. 2010; 62:14–18. [PubMed: 19937972]

Bolanos JP, Almeida A, Moncada S. Glycolysis: a bioenergetic or a survival pathway? Trends Biochem Sci. 2010; 35:145–149. [PubMed: 20006513]

Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001; 414:813–820. [PubMed: 11742414]

Brownlee M, Vlassara H, Kooney A, Ulrich P, Cerami A. Aminoguanidine prevents diabetes-induced arterial wall protein cross-linking. Science. 1986; 232:1629–1632. [PubMed: 3487117]

Bubber P, Haroutunian V, Fisch G, Blass JP, Gibson GE. Mitochondrial abnormalities in Alzheimer brain: Mechanistic implications. Annals of Neurology. 2005; 57:695–703. [PubMed: 15852400]

Burchell VS, Gandhi S, Deas E, Wood NW, Abramov AY, Plun-Favreau H. Targeting mitochondrial dysfunction in neurodegenerative disease: Part II. Expert Opinion on Therapeutic Targets. 2010; 14:497–511. [PubMed: 20334487]

Butterworth RF, Besnard AM. Thiamine-dependent enzyme changes in temporal cortex of patients with Alzheimer's disease. Metabolic Brain Disease. 1990; 5:179–184. [PubMed: 2087217]

Calingasan NY, Ho DJ, Wille EJ, Campagna MV, Ruan J, Dumont M, Yang L, Shi Q, Gibson GE, Beal MF. Influence of mitochondrial enzyme deficiency on adult neurogenesis in mouse models of neurodegenerative diseases. Neuroscience. 2008; 153:986–996. [PubMed: 18423880]

Calingasan NY, Uchida K, Gibson GE. Protein-Bound Acrolein. Journal of Neurochemistry. 1999; 72:751–756. [PubMed: 9930749]

Citron M. Alzheimer's disease: strategies for disease modification. Nat Rev Drug Discov. 2010; 9:387–398. [PubMed: 20431570]

Craft S, Baker LD, Montine TJ, Minoshima S, Watson GS, Claxton A, Arbuckle M, Callaghan M, Tsai E, Plymate SR, Green PS, Leverenz J, Cross D, Gerton B. Intranasal Insulin Therapy for Alzheimer Disease and Amnestic Mild Cognitive Impairment: A Pilot Clinical Trial. Arch Neurol. 2012; 69:29–38. [PubMed: 21911655]

Demars M, Hu Y-S, Gadadhar A, Lazarov O. Impaired neurogenesis is an early event in the etiology of familial Alzheimer's disease in transgenic mice. Journal of Neuroscience Research. 2010 9999, NA.

Depeint F, Shangari N, Furrer R, Bruce WR, O'Brien PJ. Marginal thiamine deficiency increases oxidative markers in the plasma and selected tissues in F344 rats. Nutrition Research. 2007; 27:698–704.

Du XL, Edelstein D, Dimmeler S, Ju Q, Sui C, Brownlee M. Hyperglycemia inhibits endothelial nitric oxide synthase activity by posttranslational modification at the Akt site. The Journal of Clinical Investigation. 2001; 108:1341–1348. [PubMed: 11696579]

Dumont M, Beal MF. Neuroprotective strategies involving ROS in Alzheimer disease. Free Radical Biology and Medicine. 2011; 51:1014–1026. [PubMed: 21130159]

Dumont M, Lin MT, Beal MF. Mitochondria and Antioxidant Targeted Therapeutic Strategies for Alzheimer's Disease. Journal of Alzheimer's Disease. 2010; 20:633–643.

Eckert A, Schmitt K, Götz J. Mitochondrial dysfunction – the beginning of the end in Alzheimer's disease? Separate and synergistic modes of tau and amyloid-β toxicity. Alzheimer's Research & Therapy. 2011; 3:1–11.

Frank T, Bitsch R, Maiwald J, Stein G. High thiamine diphosphate concentrations in erythrocytes can be achieved in dialysis patients by oral administration of benfotiamine. European Journal of Clinical Pharmacology. 2000; 56:251–257. [PubMed: 10952481]

Gibson G, Barclay L, Blass J. The role of the cholinergic system in thiamin deficiency. Annals of the New York Academy of Sciences. 1982; 378:382–403. [PubMed: 7044229]

Gibson GE, Blass JP. Inhibition of acetylcholine synthesis and of carbohydrate utilization by maple-syrup-urine disease metabolites. J Neurochem. 1976; 26:1073–1078. [PubMed: 945329]

Gibson GE, Chen HL, Xu H, Qiu L, Xu Z, Denton TT, Shi Q. Deficits in the mitochondrial enzyme alpha-ketoglutarate dehydrogenase lead to Alzheimer's disease-like calcium dysregulation. Neurobiol Aging. 2011

Gibson GE, Haroutunian V, Zhang H, Park LC, Shi Q, Lesser M, Mohs RC, Sheu RK, Blass JP. Mitochondrial damage in Alzheimer's disease varies with apolipoprotein E genotype. Ann Neurol. 2000; 48:297–303. [PubMed: 10976635]

Gibson GE, Jope R, Blass JP. Decreased synthesis of acetylcholine accompanying impaired oxidation of pyruvic acid in rat brain minces. Biochem J. 1975; 148:17–23. [PubMed: 1156396]

Gibson GE, Ksiezak-Reding H, Sheu K-FR, Mykytyn V, Blass JP. Correlation of enzymatic, metabolic, and behavioral deficits in thiamin deficiency and its reversal. Neurochemical Research. 1984; 9:803–814. [PubMed: 6149477]

Gibson GE, Park LCH, Zhang HUI, Sorbi S, Calingasan NY. Oxidative Stress and a Key Metabolic Enzyme in Alzheimer Brains, Cultured Cells, and an Animal Model of Chronic Oxidative Deficits. Annals of the New York Academy of Sciences. 1999; 893:79–94. [PubMed: 10672231]

Gibson GE, Peterson C. Calcium and the aging nervous system. Neurobiol Aging. 1987; 8:329–343. [PubMed: 3306433]

Gibson GE, Sheu K-FR, Blass JP, Baker A, Carlson KC, Harding B, Perrino P. Reduced Activities of Thiamine-Dependent Enzymes in the Brains and Peripheral Tissues of Patients With Alzheimer's Disease. Arch Neurol. 1988; 45:836–840. [PubMed: 3395256]

Gibson GE, Zhang H, Sheu KFR, Bogdanovich N, Lindsay JG, Lannfelt L, Vestling M, Cowburn RF. α-ketoglutarate dehydrogenase in alzheimer brains bearing the APP670/671 mutation. Annals of Neurology. 1998; 44:676–681. [PubMed: 9778267]

Gold M, Hauser RA, Chen MF. Plasma Thiamine Deficiency Associated with Alzheimer's Disease but Not Parkinson's Disease. Metabolic Brain Disease. 1998; 13:43–53. [PubMed: 9570639]

Hakim AM, Pappius HM. Sequence of metabolic, clinical, and histological events in experimental thiamine deficiency. Ann Neurol. 1983; 13:365–375. [PubMed: 6838172]

Hammes HP, Du X, Edelstein D, Taguchi T, Matsumura T, Ju Q, Lin J, Bierhaus A, Nawroth P, Hannak D, Neumaier M, Bergfeld R, Giardino I, Brownlee M. Benfotiamine blocks three major pathways of hyperglycemic damage and prevents experimental diabetic retinopathy. Nat Med. 2003; 9:294–299. [PubMed: 12592403]

Hata T, Stirling Meyer J, Tanahashi N, Ishikawa Y, Imai A, Shinohara T, Velez M, Fann WE, Kandula P, Sakai F. Three-Dimensional Mapping of Local Cerebral Perfusion in Alcoholic Encephalopathy With and Without Wernicke-Korsakoff Syndrome. J Cereb Blood Flow Metab. 1987; 7:35–44. [PubMed: 3805163]

Hazell AS, Butterworth RF, Hakim AM. Cerebral Vulnerability Is Associated with Selective Increase in Extracellular Glutamate Concentration in Experimental Thiamine Deficiency. Journal of Neurochemistry. 1993; 61:1155–1158. [PubMed: 8103080]

Herrero-Mendez A, Almeida A, Fernandez E, Maestre C, Moncada S, Bolanos JP. The bioenergetic and antioxidant status of neurons is controlled by continuous degradation of a key glycolytic enzyme by APC/C-Cdh1. Nat Cell Biol. 2009; 11:747–752. [PubMed: 19448625]

Ito E, Oka K, Etcheberrigaray R, Nelson TJ, McPhie DL, Tofel-Grehl B, Gibson GE, Alkon DL. Internal Ca2+ mobilization is altered in fibroblasts from patients with Alzheimer disease. Proc Natl Acad Sci U S A. 1994; 91:534–538. [PubMed: 8290560]

Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. The Lancet Neurology. 2010; 9:119–128.

Jono T, Kimura T, Takamatsu J, Nagai R, Miyazaki K, Yuzuriha T, Kitamura T, Horiuchi S. Accumulation of imidazolone, pentosidine and N(epsilon)-(carboxymethyl)lysine in hippocampal CA4 pyramidal neurons of aged human brain. Pathol Int. 2002; 52:563–571. [PubMed: 12406185]

Karuppagounder SS, Xu H, Shi Q, Chen LH, Pedrini S, Pechman D, Baker H, Beal MF, Gandy SE, Gibson GE. Thiamine deficiency induces oxidative stress and exacerbates the plaque pathology in Alzheimer's mouse model. Neurobiology of Aging. 2009; 30:1587–1600. [PubMed: 18406011]

Kauffman FC. The quantitative histochemistry of enzymes of the pentose phosphate pathway in the central nervous system of the rat. Journal of Neurochemistry. 1972; 19:1–9. [PubMed: 5009897]

Ke ZJ, Gibson GE. Selective response of various brain cell types during neurodegeneration induced by mild impairment of oxidative metabolism. Neurochem Int. 2004; 45:361–369. [PubMed: 15145550]

Kopelman MD. Frontal dysfunction and memory deficits in the alcoholic korsakoff syndrome and alzheimer-type dementia. Brain. 1991; 114A:117–137. [PubMed: 1998878]

Krautwald M, Munch G. Advanced glycation end products as biomarkers and gerontotoxins – A basis to explore methylglyoxal-lowering agents for Alzheimer's disease? Exp Gerontol. 2010; 45:744–751. [PubMed: 20211718]

La Selva M, Beltramo E, Pagnozzi F, Bena E, Molinatti PA, Molinatti GM, Porta M. Thiamine corrects delayed replication and decreases production of lactate and advanced glycation end-products in bovine retinal and human umbilical vein endothelial cells cultured under high glucose conditions. Diabetologia. 1996; 39:1263–1268. [PubMed: 8932990]

Langbaum JBS, Chen K, Lee W, Reschke C, Bandy D, Fleisher AS, Alexander GE, Foster NL, Weiner MW, Koeppe RA, Jagust WJ, Reiman EM. Categorical and correlational analyses of baseline fluorodeoxyglucose positron emission tomography images from the Alzheimer's Disease Neuroimaging Initiative (ADNI). NeuroImage. 2009; 45:1107–1116. [PubMed: 19349228]

Leissring MA, Akbari Y, Fanger CM, Cahalan MD, Mattson MP, LaFerla FM. Capacitative calcium entry deficits and elevated luminal calcium content in mutant presenilin-1 knockin mice. J Cell Biol. 2000; 149:793–798. [PubMed: 10811821]

Liu F, Iqbal K, Grundke-Iqbal I, Hart GW, Gong C-X. O-GlcNAcylation regulates phosphorylation of tau: A mechanism involved in Alzheimer's disease. Proceedings of the National Academy of Sciences of the United States of America. 2004; 101:10804–10809. [PubMed: 15249677]

Loew D. Pharmacokinetics of thiamine derivatives especially of benfotiamine. Int J Clin Pharmacol Ther. 1996; 34:47–50. [PubMed: 8929745]

Lonsdale D. A Review of the Biochemistry, Metabolism and Clinical Benefits of Thiamin(e) and Its Derivatives. eCAM. 2006; 3:49–59. [PubMed: 16550223]

Loske C, Gerdemann A, Schepl W, Wycislo M, Schinzel R, Palm D, Riederer P, Munch G. Transition metal-mediated glycoxidation accelerates cross-linking of beta-amyloid peptide. Eur J Biochem. 2000; 267:4171–4178. [PubMed: 10866821]

Loske C, Neumann A, Cunningham AM, Nichol K, Schinzel R, Riederer P, Munch G. Cytotoxicity of advanced glycation endproducts is mediated by oxidative stress. J Neural Transm. 1998; 105:1005–1015. [PubMed: 9869332]

Manczak M, Mao P, Calkins MJ, Cornea A, Reddy AP, Murphy MP, Szeto HH, Park B, Reddy PH. Mitochondria-Targeted Antioxidants Protect Against Amyloid-β Toxicity in Alzheimer's Disease Neurons. Journal of Alzheimer's Disease. 2010; 20:609–631.

Meador K, Loring D, Nichols M, Zamrini E, Rivner M, Posas H, Thompson E, Moore E. Preliminary Findings of High-Dose Thiamine in Dementia of Alzheimer's Type. Journal of Geriatric Psychiatry and Neurology. 1993; 6:222–229. [PubMed: 8251051]

Meyer JS, Tanahashi N, Ishikawa Y, Hata T, Velez M, Farm WE, Kandula P, Mortel KF, Rogers RL. Cerebral Atrophy and Hypoperfusion Improve During Treatment of Wernicke-Korsakoff Syndrome. J Cereb Blood Flow Metab. 1985; 5:376–385. [PubMed: 4030916]

Micheau J, Durkin TP, Destrade C, Rolland Y, Jaffard R. Chronic administration of sulbutiamine improves long term memory formation in mice: Possible cholinergic mediation. Pharmacology Biochemistry and Behavior. 1985; 23:195–198.

Mimori Y, Katsuoka H, Nakamura S. Thiamine therapy in Alzheimer's disease. Metab Brain Dis. 1996; 11:89–94. [PubMed: 8815393]

Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993; 43:2412–2414. [PubMed: 8232972]

Munch G, Shepherd CE, McCann H, Brooks WS, Kwok JB, Arendt T, Hallupp M, Schofield PR, Martins RN, Halliday GM. Intraneuronal advanced glycation endproducts in presenilin-1 Alzheimer's disease. Neuroreport. 2002; 13:601–604. [PubMed: 11973454]

Netzel M, Ziems M, Jung KH, Noll E, Borsch C, Bitsch I. Effect of high-dosed thiamine hydrochloride and S-benzoyl-thiamine-O-monophosphate on thiamine-status after chronic ethanol administration. Biofactors. 2000; 11:111–113. [PubMed: 10705978]

Nolan KA, Black RS, Sheu KF, Langberg J, Blass JP. A trial of thiamine in Alzheimer's disease. Arch Neurol. 1991; 48:81–83. [PubMed: 1986730]

Novello F, McLean P. The pentose phosphate pathway of glucose metabolism. Measurement of the non-oxidative reactions of the cycle. Biochem J. 1968; 107:775–791. [PubMed: 16742603]

Ollat H, Laurent B, Bakchine S, Michel BF, Touchon J,B,D. Effects of the association of sulbutiamine with an acetylcholinesterase inhibitor in early stage and moderate Alzheimer disease. Encephale. 2007; 33:211–215. [PubMed: 17675917]

Pan X, Gong N, Zhao J, Yu Z, Gu F, Chen J, Sun X, Zhao L, Yu M, Xu Z, Dong W, Qin Y, Fei G, Zhong C, Xu T-L. Powerful beneficial effects of benfotiamine on cognitive impairment and {beta}-amyloid deposition in amyloid precursor protein/presenilin-1 transgenic mice. Brain. 2010a; 133:1342–1351. [PubMed: 20385653]

Pan X, Gong N, Zhao J, Yu Z, Gu F, Chen J, Sun X, Zhao L, Yu M, Xu Z, Dong W, Qin Y, Fei G, Zhong C, Xu TL. Powerful beneficial effects of benfotiamine on cognitive impairment and beta-amyloid deposition in amyloid precursor protein/presenilin-1 transgenic mice. Brain. 2010b; 133:1342–1351. [PubMed: 20385653]

Park LC, Calingasan NY, Uchida K, Zhang H, Gibson GE. Metabolic impairment elicits brain cell type-selective changes in oxidative stress and cell death in culture. J Neurochem. 2000; 74:114–124. [PubMed: 10617112]

Park LCH, Zhang H, Sheu K-FR, Calingasan NY, Kristal BS, Gordon Lindsay J, Gibson GE. Metabolic Impairment Induces Oxidative Stress, Compromises Inflammatory Responses, and Inactivates a Key Mitochondrial Enzyme in Microglia. Journal of Neurochemistry. 1999; 72:1948–1958. [PubMed: 10217272]

Pekovich SR, Martin PR, Singleton CK. Thiamine Deficiency Decreases Steady-State Transketolase and Pyruvate Dehydrogenase but not alpha -Ketoglutarate Dehydrogenase mRNA Levels in Three Human Cell Types. J. Nutr. 1998; 128:683–687. [PubMed: 9521628]

Praticò D, Uryu K, Leight S, Trojanoswki JQ, Lee VM-Y. Increased Lipid Peroxidation Precedes Amyloid Plaque Formation in an Animal Model of Alzheimer Amyloidosis. The Journal of Neuroscience. 2001; 21:4183–4187. [PubMed: 11404403]

Rafii M, Aisen P. Recent developments in Alzheimer's disease therapeutics. BMC Medicine. 2009; 7:7. [PubMed: 19228370]

Reggiani C, Patrini C, Rindi G. Nervous tissue thiamine metabolism in vivo. I. Transport of thiamine and thiamine monophosphate from plasma to different brain regions of the rat. Brain Research. 1984; 293:319–327. [PubMed: 6697223]

Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, Saunders AM, Hardy J. Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. Proc Natl Acad Sci U S A. 2004; 101:284–289. [PubMed: 14688411]

Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ. Memantine in Moderate-to-Severe Alzheimer's Disease. New England Journal of Medicine. 2003; 348:1333–1341. [PubMed: 12672860]

Rodriguez JJ, Jones VC, Tabuchi M, Allan SM, Knight EM, LaFerla FM, Oddo S, Verkhratsky A. Impaired adult neurogenesis in the dentate gyrus of a triple transgenic mouse model of Alzheimer's disease. PLoS One. 2008; 3:e2935. [PubMed: 18698410]

Schenk G, Duggleby RG, Nixon PF. Properties and functions of the thiamin diphosphate dependent enzyme transketolase. Int J Biochem Cell Biol. 1998; 30:1297–1318. [PubMed: 9924800]

Shangari N, Bruce WR, Poon R, O'Brien PJ. Toxicity of glyoxals--role of oxidative stress, metabolic detoxification and thiamine deficiency. Biochem. Soc. Trans. 2003; 31:1390–1393. [PubMed: 14641070]

Shangari N, Depeint F, Furrer R, Bruce WR, O'Brien PJ. The effects of partial thiamin deficiency and oxidative stress (i.e., glyoxal and methylglyoxal) on the levels of [alpha]-oxoaldehyde plasma protein adducts in Fischer 344 rats. FEBS Letters. 2005; 579:5596–5602. [PubMed: 16214141]

Shi Q, Gibson GE. Up-regulation of the mitochondrial malate dehydrogenase by oxidative stress is mediated by miR-743a. J Neurochem. 2011

Sourris KC, Harcourt BE, Forbes JM. A new perspective on therapeutic inhibition of advanced glycation in diabetic microvascular complications: common downstream endpoints achieved through disparate therapeutic approaches? Am J Nephrol. 2009; 30:323–335. [PubMed: 19556753]

Starkov AA, Fiskum G, Chinopoulos C, Lorenzo BJ, Browne SE, Patel MS, Beal MF. Mitochondrial alpha-ketoglutarate dehydrogenase complex generates reactive oxygen species. J Neurosci. 2004; 24:7779–7788. [PubMed: 15356189]

Stracke H, Gaus W, Achenbach U, Federlin K, Bretzel RG. Benfotiamine in Diabetic Polyneuropathy (BENDIP): Results of a Randomised, Double Blind, Placebo-controlled Clinical Study. Exp Clin Endocrinol Diabetes. 2008; 116:600–605. [PubMed: 18473286]

Stracke H, Hammes HP, Werkmann D, Mavrakis K, Bitsch I, Netzel M, Geyer J, Kopcke W, Sauerland C, Bretzel RG, Federlin KF. Efficacy of benfotiamine versus thiamine on function and glycation products of peripheral nerves in diabetic rats. Exp Clin Endocrinol Diabetes. 2001; 109:330–336. [PubMed: 11571671]

Sudarsan N, Cohen-Chalamish S, Nakamura S, Emilsson GM, Breaker RR. Thiamine Pyrophosphate Riboswitches Are Targets for the Antimicrobial Compound Pyrithiamine. Chemistry & Biology. 2005; 12:1325–1335. [PubMed: 16356850]

Thornalley PJ, Jahan I, Ng R. Suppression of the accumulation of triosephosphates and increased formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in vitro. J Biochem. 2001; 129:543–549. [PubMed: 11275553]

Thorpe SR, Baynes JW. Role of the Maillard reaction in diabetes mellitus and diseases of aging. Drugs Aging. 1996; 9:69–77. [PubMed: 8820792]

Torres LL, Quaglio NB, de Souza GT, Garcia RT, Dati LMM, Moreira WL, de Melo Loureiro AP, de souza-Talarico JN, Smid J, Porto CS, de Campos Bottino CM, Nitrini R, de Moraes Barros SB, Camarini R, Marcourakis T. Peripheral Oxidative Stress Biomarkers in Mild Cognitive Impairment and Alzheimer's Disease. Journal of Alzheimer's Disease. 2011; 26:59–68.

Tretter L, Adam-Vizi V. Generation of reactive oxygen species in the reaction catalyzed by alpha-ketoglutarate dehydrogenase. J Neurosci. 2004; 24:7771–7778. [PubMed: 15356188]

Voloboueva LA, Lee SW, Emery JF, Palmer TD, Giffard RG. Mitochondrial Protection Attenuates Inflammation-Induced Impairment of Neurogenesis In Vitro and In Vivo. J. Neurosci. 2010; 30:12242–12251. [PubMed: 20844120]

Volvert M-L, Seyen S, Piette M, Evrard B, Gangolf M, Plumier J-C, Bettendorff L. Benfotiamine, a synthetic S-acyl thiamine derivative, has different mechanisms of action and a different pharmacological profile than lipid-soluble thiamine disulfide derivatives. BMC Pharmacology. 2008; 8:10. [PubMed: 18549472]

Wang Z, Pandey A, Hart GW. Dynamic Interplay between O-Linked N-Acetylglucosaminylation and Glycogen Synthase Kinase-3-dependent Phosphorylation. Molecular & Cellular Proteomics. 2007; 6:1365–1379. [PubMed: 17507370]

Witt ED, Goldman-Rakic PS. Intermittent thiamine deficiency in the rhesus monkey. II. Evidence for memory loss. Annals of Neurology. 1983; 13:396–401. [PubMed: 6404215]

Wong CY, Qiuwaxi J, Chen H, Li SW, Chan HT, Tam S, Shu XO, Lau CP, Kwong YL, Tse HF. Daily intake of thiamine correlates with the circulating level of endothelial progenitor cells and the endothelial function in patients with type II diabetes. Molecular Nutrition & Food Research. 2008; 52:1421–1427. [PubMed: 18925614]

Zhang Q, Yang G, Li W, Fan Z, Sun A, Luo J, Ke Z-J. Thiamine deficiency increases [beta]-secretase activity and accumulation of [beta]-amyloid peptides. Neurobiology of Aging. 2011; 32:42–53. [PubMed: 19233513]

Zhao J, Sun X, Yu Z, Pan X, Gu F, Chen J, Dong W, Zhao L, Zhong C. Exposure to Pyrithiamine Increases β-Amyloid Accumulation, Tau Hyperphosphorylation, and Glycogen Synthase Kinase-3 Activity in the Brain. Neurotoxicity Research. 2011; 19:575–583. [PubMed: 20567953]

Ziems M, Netzel M, Bitsch I. Biokinetic parameters and metabolism of S-benzoylthiamine-O-monophosphate. Biofactors. 2000; 11:109–110. [PubMed: 10705977]

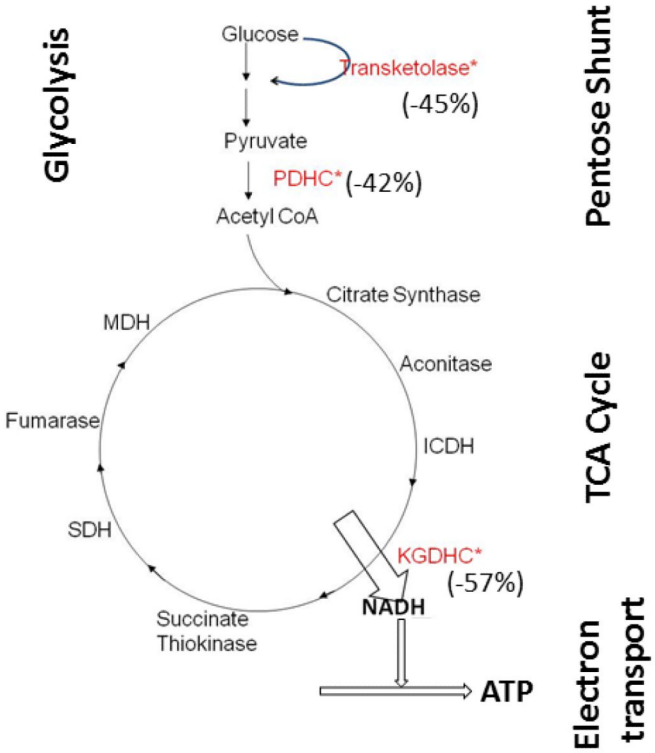

Figure 1.

Normal brain metabolism depends on thiamine dependent processes that are diminished in patients with AD. The thiamine dependent processes are in red and marked with an *. The percents are the reduction in autopsy brains of patients that died with AD.

The abbreviations are as follows: PDHC (pyruvate dehydrogenase complex), KGDHC (α-ketoglutarate dehydrogenase complex), ICDHC (isocitrate dehydrogenase complex), SDH (succinate dehydrogenase), MDH (malate dehydrogenase).

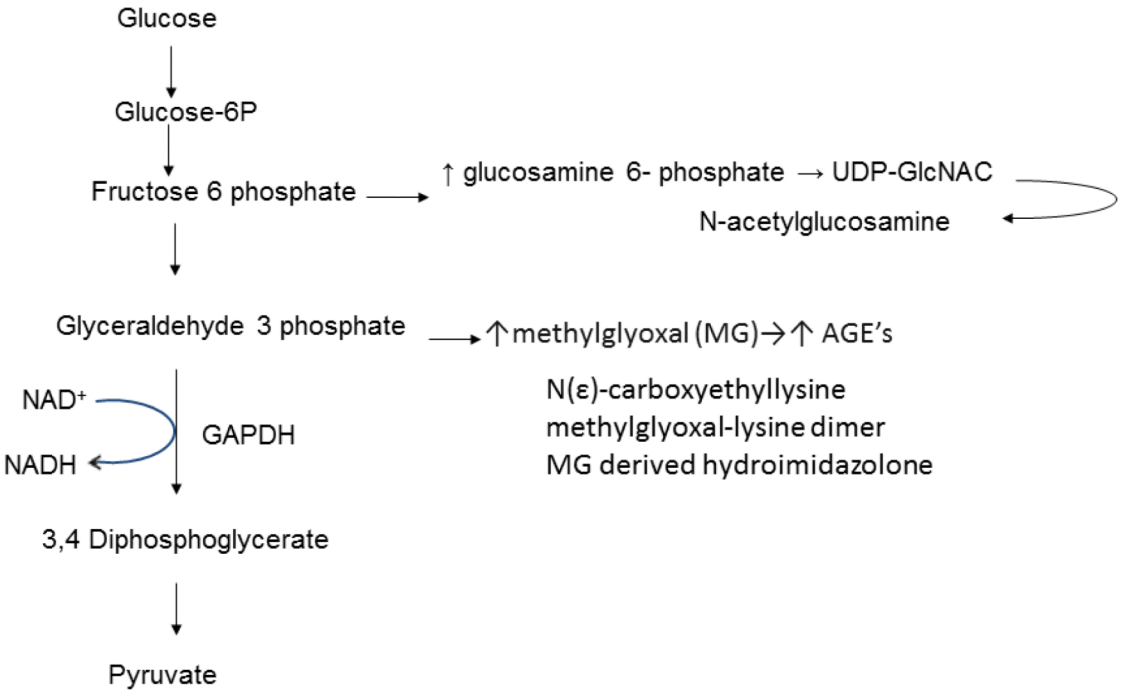

Figure 2.
Oxidant induced inhibition of the glycolytic enyzme glyceraldehyde-3-phosphate dehydrogenase (GAPDH) leads to accumulation of toxic metabolites. UDP-GlcNAc refers to uridine diphosphate N-acetylglucosamine

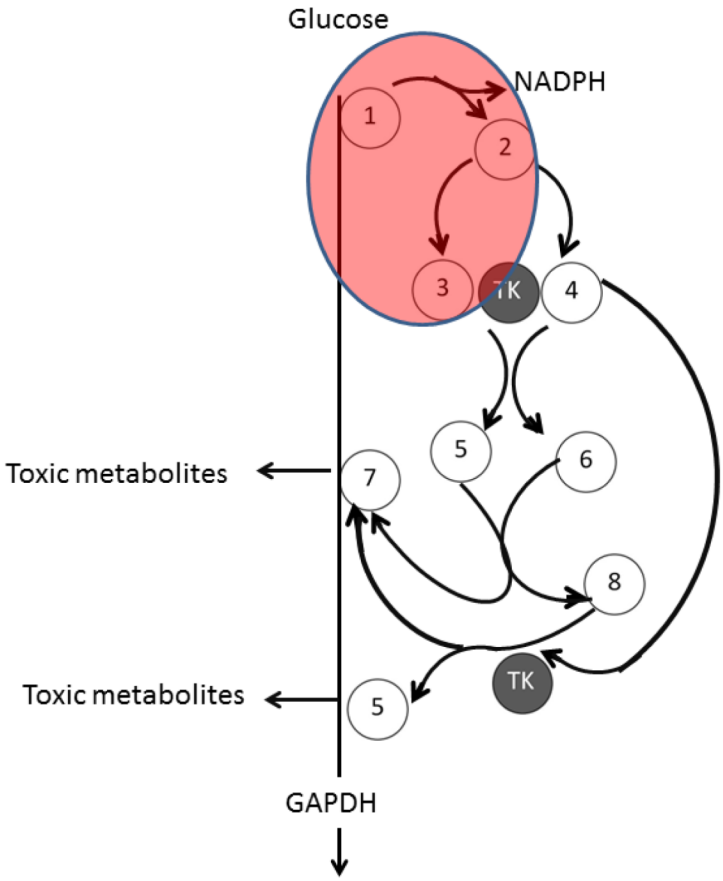

Figure 3.
The interactions of the pentose shunt with glycolysis and toxic metabolites. The numbers refer to the metabolites of the pentose shunt.
1 Glucose-6-phosphate
2. Ribulose -5- phosphate
3. Ribose-5-phosphate
4 Xylulose-5-phosphate
5 Glyceraldehyde-3-phosphate
6. Sedoheptulose-7-phosphate
7 Fructose6-phosphate
8. Erythrose-4-phosphate
GAPDH refers to glyceraldehydes-3-phosphate dehydrogenase
TK refers to transketolase

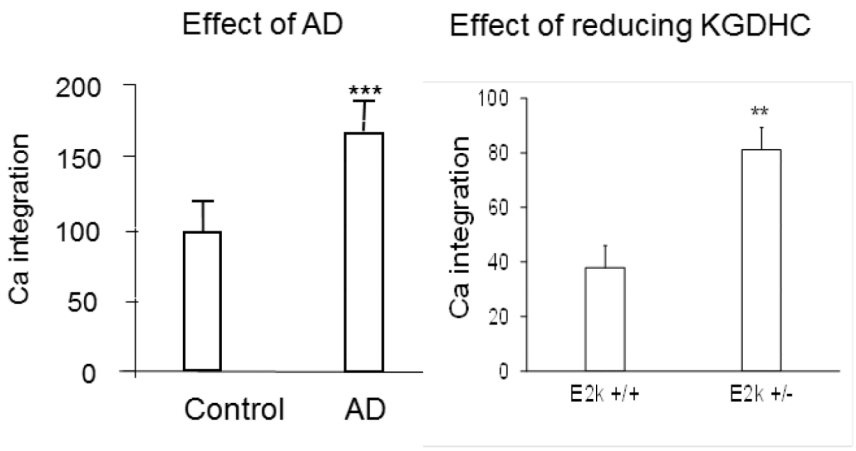

Figure 4.
Endoplasmic reticulum (ER) calcium stores are exaggerated in fibroblasts from AD patients and in neurons deficient in KGDHC.

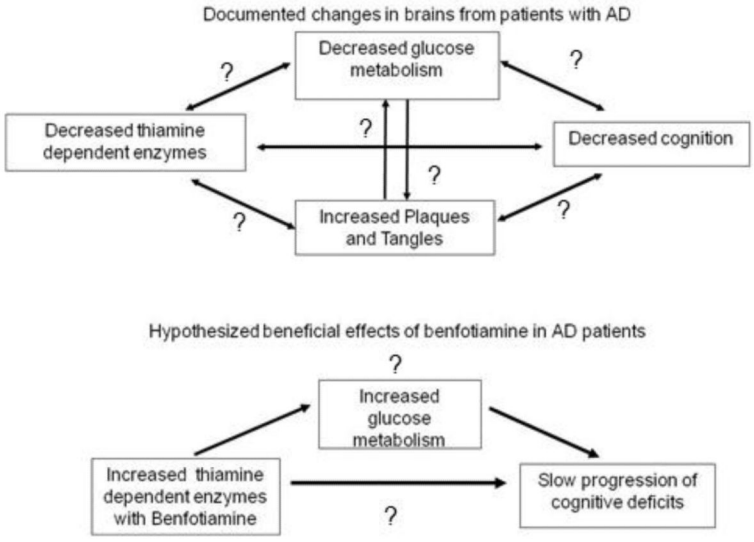

Figure 5.

Thiamine derivatives may provide more bio-available thiamine than thiamine itself.

Thiamine contains an aminopyrimidine ring and a thiazole ring with methyl and hydroxyethyl side chains linked by a methylene bridge

Fursultiamine*N*-[(4-amino-2-methylpyrimidin-5-yl)methyl]-*N*-{(1*E*)-4-hydroxy-1-methyl-2-[(tetrahydrofuran-2-ylmethyl)disulfanyl]but-1-en-1-yl}formamide

Sulbutiamine[4-[(4-amino-2-methyl-pyrimidin-5-yl)methyl-formyl-amino]-3-[2-[(4-amino-2-methyl-pyrimidin-5-yl)methyl-formyl-amino]-5-(2-methylpropanoyloxy)pent-2-en-3-yl]disulfanyl-pent-3-enyl] 2-methylpropanoate

BenfotiamineS-[(2Z)-2-{[(4-amino-2-methylpyrimidin-5-yl)methyl] (formyl)amino}-5-(phosphonooxy)pent-2-en-3-yl] benzenecarbothioate.

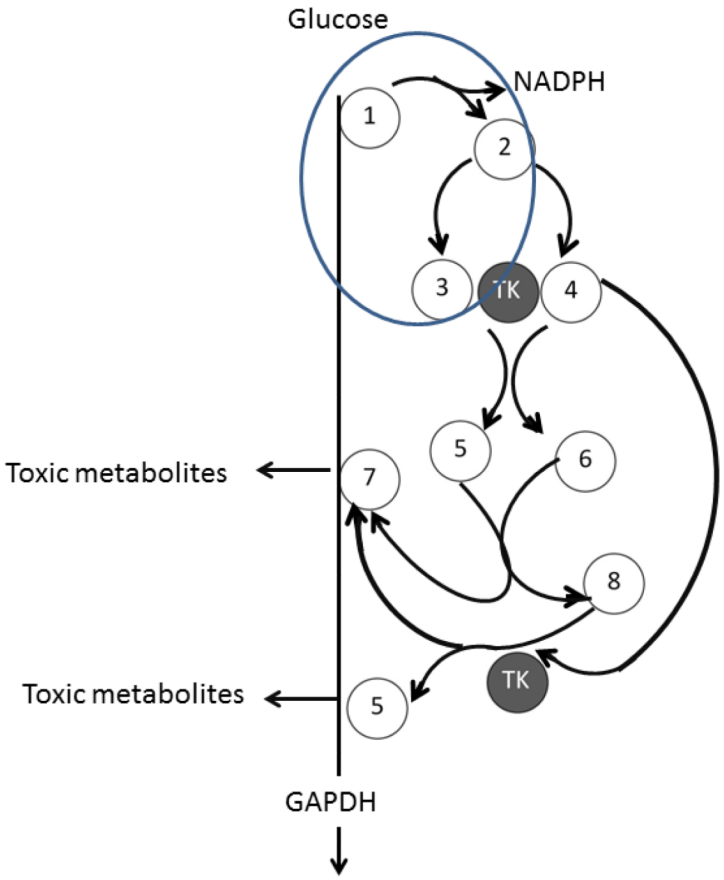

Figure 6.
Role of thiamine dependent processes in AD and their potential reversal by benfotiamine.