

# The Role of Thiamine in Wilson's Disease: Possible Genetic and Cellular Signaling Mechanisms

Khanh vinh quoc Lương\* and Lan Thi Hoang Nguyen

Vietnamese American Medical Research Foundation, Westminster, California, USA

## Abstract

The relationship between supplemental thiamine and Wilson's disease has been the focus of recent investigation; and supplemental thiamine has been reported to modulate Wilson's disease. Genetic studies have helped identify a number of factors that link thiamine to Wilson's disease, including transcription factor p53, Bcl-2, caspase-2, heme oxygenase-1, and apolipo protein E. Thiamine has also been implicated in Wilson's disease through its effects on serotonin, reactive oxygen species, and nitric oxide synthase. Therefore, further investigations of thiamine in Wilson's disease are needed to clarify this relationship.

**Keywords:** Thiamine; Wilson's disease; Vitamin B1; Transketolase; Copper toxicity

## Introduction

Copper is an essential trace element that is required for the function of enzymes, including cytochrome c oxidase, superoxide dismutase, dopamine  $\beta$ -hydroxylase, lysyl oxidase, and ceruloplasmin. Disturbances in copper hemostasis result in cell death in the liver and the Central Nervous System (CNS) in Wilson's disease [1]. During the course of Wilson's disease, copper accumulates equally in different parts of the brain compared with control subjects [2]. Copper ions may directly stimulate the proliferation of hepatic stellate cells via oxidative stress [3]. The relationship between thiamine and copper was reported in the literature. A low serum ceruloplasmin concentration is considered diagnostic for Wilson's disease [4]. The serum ceruloplasmin level, which serves as a marker of copper metabolism, is also decreased in Thiamine-Deficient (TD) animals [5]. Copper can cause thiamine to be oxidized to the fluorescent products thiochrome and oxodihydrothiochrome in neutral and acidic media [6]. Copper also induces neuronal death in murine neocortical cell cultures; the addition of thiamine to the drinking water of an animal model with Wilson's disease markedly extends the animal's life span from 6 months to greater than 16 months [7]. Copper induces proteotoxic effects, inflammatory reactions/oxidative stress, growth arrest, and DNA damage in human liver carcinoma cells [8]. Hepatic copper accumulation significantly increases the risk of cancerous neoplasms both in humans and rats [9]. However, oral thiamine supplementation attenuates Wilson's disease-induced hepatocellular carcinoma [10]. In addition, copper overload induces lipid peroxidation, the formation of 4-hydroxy-nonenal (HNE), and mitochondrial dysfunction in rats [11]. HNE inhibits Pyruvate Dehydrogenase (PDH) and  $\alpha$ -ketoglutarate dehydrogenase (KGDH) [12,13], and thiamine improves the activity of these enzymes [13-15]. Thiamin pyrophosphate (TPP) inhibits PDH kinase, which phosphorylates and reduces PDH activity [16]. Thiamine deficiency reduces the activity of the thiamine dependent-enzymes KGDHC and PDH and also induces regional selective neurodegeneration [17-19]. Thiamine and TPP have been used in patients with PDH deficiency [20-24] and KGDH deficiency diseases [25-27]. Taken together, these findings suggest that there is a relationship between thiamine and Wilson's disease. Therefore, in this work, we review the role of thiamine in Wilson's disease.

## The Genomic Factors Associated with Thiamine In Cancer

The p53 gene and protein play a critical role in the regulation of the normal cell cycle, cell cycle arrest, and the apoptotic response. p53 is a transcription factor with a major role in determining cell fate in response to DNA damage. Treating human liver cells with copper, results in a significant elevation of p53 levels that is accompanied by evidence of apoptosis [28]. Copper induces apoptosis in epithelial breast cancer MCF-7 cells independently of the caspases, and a functional p53 is required for apoptosis in these epithelial cells [29]. Increased p53 mutations were observed in liver samples from patients with Wilson's disease [30], and an increased p53 mutation load was suggested to predispose individuals with Wilson's disease to the development of cancer [31]. However, increased Thiamine Transporter (ThTr) levels are observed in cells that over-express mThTr-1 or in cells that have been exposed to conditions that induce DNA damage or p53 activation [32]. Thiamine diphosphate (TDP) inhibits p53 binding, and thiamine inhibits intracellular p53 activity [33]. p53 expression is significantly decreased in cultured retinal neurons of diabetic rats treated with thiamine compared with controls [34]. These observations suggest that the transcription factor p53 is activated in Wilson's disease and show that there is an increasing apoptotic response to cellular damage. These observations also suggest that thiamine ameliorates these effects.

Bcl-2 is a membrane-bound protein that plays a neuron-protective role in the CNS. Bcl-2 inhibits apoptosis and enhances the survival of newborn neurons in the normal and ischemic hippocampus [35]. Bcl-2 mRNA and protein expression are developmentally regulated in both the human and murine brain [36,37]. Bcl-2 inhibits the death of a central neural cell line due to serum and growth factor withdrawal, the calcium ionophore A23187, glucose withdrawal, membrane peroxidation, and

**\*Corresponding author:** Khanh vinh quoc Lương, Vietnamese American Medical Research Foundation, Westminster, California, USA, Tel: 714 839 5898; Fax: 714 839 5989; E-mail: [Lng2687765@aol.com](mailto:Lng2687765@aol.com)

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in some cases, free-radical-induced damage [38]. Using human M17 neuroblastoma cells as a model to examine copper toxicity, copper-glycine reduced Bcl-2 expression by 50% compared with glycine-treated cells [39]. As excessive copper ingestion is further prolonged, copper levels in the liver and serum and the alanine aminotransferase (ALT) level in serum rise, and apoptotic cells appear in the liver. Bax and Bcl-2 expression significantly increase and progressively increase with further prolonged excessive copper ingestion in rat models of hepatolenticular degeneration compared with controls fed a normal diet [40]. However, pre-treatment with B vitamins (B<sub>1</sub>, B<sub>6</sub>, and B<sub>12</sub>) has a protective effect in the brain of mice with experimentally induced epilepsy, with an early induction of Bcl-2 expression within 12 hours of the epileptic episode [41]. Thiamine deprivation increases cell death and reduces Bcl-2 expression during hybridoma cell culture [42]. Benfotiamine is a transketolase activator that directs glucose to the pentose phosphate pathway and improves the functional recovery of an infarcted heart by increasing Bcl-2 protein levels [43]. When human and bovine pericytes are intermittently exposed to high glucose, there is a 50-60% decrease in the Bcl-2 to Bax ratio for both expression and concentration; the addition of thiamine and benfotiamine completely reverses this damaging effect [44]. Taken together, these findings suggest that thiamine may play a neuron-protective role in Wilson's disease by increasing the apoptotic inhibitor Bcl-2.

Caspases are cysteinyl aspartate-specific proteases that play a critical role in the regulatory and execution phases of apoptosis [45]. Increased caspase-3 activity is consistently reported in the cortex of Long-Evans Cinnamon (LEC) rats [46]. The addition of 20  $\mu$ M copper for 22 hours to murine neocortical cell cultures decreases the ATP levels and induces neuronal death without glial death. This selective neuronal death is associated with the activation of caspase-3 and is reduced by free radical scavengers; the addition of thiamine reduces copper-induced neuronal death [7]. Breast cancer cells transfected with the thiamine transporter *SLC19A3* show an increase in apoptosis when exposed to doxorubicin and radiation, and the caspase-3-dependent pathway partially mediates this effect [47]. The thiamine deficiency caused by thiamine antagonists leads to caspase-3 apoptosis in the neuronally differentiated rat PC-12 cell line [48]. Benfotiamine accelerates the healing of ischemic diabetic limbs in mice via the potentiation of angiogenesis and prevention of pro-apoptotic caspase-3 induction [49]. Sulbutiamine, a highly lipid-soluble synthetic analog of thiamine, attenuates trophic factor deprivation-induced cell death in transformed Retinal Ganglion Cells (RGC-5) and decreases the expression of cleaved caspase-3 [50]. These findings suggest that thiamine may play a role in Wilson's disease by inhibiting the activity of the apoptotic factor caspase-3.

Heme oxygenase-1 (HO-1) is a stress protein that may confer cytoprotection by enhancing the catabolism of pro-oxidant heme into the radical scavenging bile pigments biliverdin and bilirubin. The HO-1 gene is susceptible to up regulation by a host of noxious stimuli and is induced in CNS tissues that are affected by neurological diseases [51]. In a normal brain, the basal HO-1 expression level is low and is restricted to small groups of scattered neurons and neuroglia [52]. Exposure of hepatocellular carcinoma cell lines (HepG2 and Hep3B cells) to Cu<sup>2+</sup> inhibits the enzymes porphobilinogen deaminase and aminolevulinic acid dehydratase of the heme synthesis pathway and, in parallel, upregulates HO-1 expression [53]. DL- $\alpha$ -lipoic acid (LA) displays an antioxidant effect on copper-induced acute hepatitis in LEC rats; LA treatment significantly suppresses the inactivation of catalase and glutathione peroxidase and the induction of HO-1, which is inducible under oxidative stress. Furthermore, LA shows a dose-dependent suppressive effect against the increase in the nonheme iron

contents of both cytosolic and crude mitochondrial fractions [54]. Similarly, thiamine deficiency produces region-specific neuronal loss and HO-1 induction in microglia [55,56]. Thiamine administration blocks further neuronal loss and the induction of HO-1-positive microglia (while other microglial changes persist) [57]. Taken together, these findings suggest that thiamine may play a role in Wilson's disease by suppressing HO-1 expression.

In women, the *apolipoprotein E (ApoE)  $\epsilon$ 4*-positive genotype is associated with an earlier onset of Wilson symptoms, particularly among *ATP-ase 7B* gene *p.H1069Q* homozygous patients [58]. The presence of *ApoE  $\epsilon$ 3/3* attenuates clinical manifestations in European subjects with Wilson's disease [59]. However, Muramatsu et al. [60] reported that the frequency of the *ApoE  $\epsilon$ 4* allele is significantly higher in TD dementia patients. These findings suggest that the *ApoE* genotype may affect both Wilson's disease and thiamine status. Table 1 illustrates the genetic role of thiamine in Wilson's disease.

### The Role of Thiamine in Wilson's Disease

Serotonin (5-HT) is an indolamine that is derived from the amino acid tryptophan and is involved in a range of behaviors and psychological processes, including mood, anxiety, obsessive-compulsive symptoms, and social interaction. Free copper in the brain is toxic and leads to neuronal and cellular damage; copper reduces N-acetyl transferase activity, which results in a decrease in N-acetyl serotonin synthesis [61]. 5-HT immuno reactive fiber densities in the cingulate cortex, caudate-putamen, hypothalamus, and hippocampus in LEC rats are significantly higher than in controls at 4, 10, and 20 weeks of age. In the cingulate cortex and caudate-putamen, 5-HT immunoreactive fiber densities gradually increase with age. The number of aberrant 5-HT immunoreactive fibers in the cingulate cortex, caudate-putamen, hypothalamus, and hippocampus of LEC rats is significantly higher than in controls [62]. In patients with Wilson's disease, depression is a frequent psychiatric symptom [63,64]. A prospective study revealed that depressive symptomatology is related to an alteration of presynaptic Serotonin Transporters (SERT) [65]. A significant negative correlation was found between the Hamilton rating scale for depression and SERT density in the thalamus-hypothalamus region of patients with Wilson's disease [66]. In addition, serotonergic system dysfunction occurs in mice fed with a TD diet; specifically, [<sup>3</sup>H]5-HT, which labels the indolaminergic fiber systems of the cerebellum, medulla, mid-brain and diencephalon, was markedly decreased compared with mice that were fed normal chow [67]. The SSRI fluvoxamine significantly inhibits depressive behavior in TD mice, as measured by an increase of immobile time in a forced swimming test [68]. Patients with low cerebrospinal fluid thiamine concentrations exhibited low 5-Hydroxyindoleacetic Acid (5-HIAA) values; however, thiamine treatment increased 5-HIAA markedly [69]. There was a significant decrease in 5-HT uptake in the synaptosomal preparations of TD rat cerebella; the administration of thiamine *in vivo* resulted in a significant reverse of the inhibition of 5-HT uptake, which coincides with a dramatic clinical improvement [70]. A pyriethiamine-induced increase in the endogenous 5-HIAA of the medulla-pons region of TD rats occurs simultaneously with the onset of neurological signs; thiamine administration reverses both trends [71]. In addition, thiamine (1-3,000  $\mu$ M) reduces <sup>3</sup>H-5-HT uptake to 83% of the control uptake levels in human placental choriocarcinoma cells. These cells are the only human cell line that expresses the 5-HT transporter [72]. Lurcher mice are characterized by considerable atrophy in the cerebellum, which is secondary to a massive loss of cerebellar Purkinje cells, granule cells, and neurons from the inferior olivary nucleus; a therapeutic combination of amantadine, thiamine, and L-tryptophan

Wilson's Disease	Thiamine
<p><b>p53 gene</b></p> <p>*Copper results in a significant elevation of p53 levels, and human liver cells showed evidence of apoptosis.</p> <p>*A p53 mutation was reported in samples of Wilson's disease.</p> <p>*An increased p53 load was suggested to predispose individuals with Wilson's disease to the development of cancer.</p>	<p>* Increased thiamine transporter activity is observed in cells that over-express the genes that code for thiamine transporters and under conditions of DNA damage or p53 activation.</p> <p>*Thiamine diphosphate inhibits p53 binding, and thiamine inhibits intracellular p53 activity.</p> <p>*The expression of p53 decreases significantly in the cultured retinal neurons from diabetic rats treated with thiamine.</p>
<p><b>Bcl-2</b></p> <p>*Bcl-2 is a membrane-bound protein that plays a neuro-protective role in the CNS.</p> <p>*Bcl-2 inhibits apoptosis and enhances the survival of newborn neurons in the normal and ischemic hippocampus</p> <p>*With a further prolonged excessive copper ingestion, copper levels in the liver and serum and the alanine aminotransferase level in serum rise, and more apoptotic cells appear in the liver.</p>	<p>*Pre-treatment with B vitamins (B<sub>1</sub>, B<sub>6</sub>, and B<sub>12</sub>) has a protective effect on experimental epilepsy in the brains of mice, with an early induction of Bcl-2 expression within 12 hours of the epileptic episode.</p> <p>*Thiamine deprivation increases cell death and reduces Bcl-2 expression in cultured hybridoma cells.</p> <p>*Benfotiamine improves the functional recovery of infarcted hearts, with increased Bcl-2 protein levels.</p> <p>*The Bcl-2 to Bax ratio decreases by 50%-60% (for both expression and concentration) in human and bovine pericytes that are intermittently exposed to high glucose; the addition of thiamine and benfotiamine completely reverses this damaging effect.</p>
<p><b>Caspases</b></p> <p>*Caspases are cysteinyl aspartate-specific proteases that play a critical role in the regulatory and execution phases of apoptosis.</p> <p>*Increased caspase-3 activity is consistently reported in the cortex of Long-Evans Cinnamon (LEC) rats.</p> <p>*The addition of 20 μM copper for 22 hours to murine neocortical cell cultures decreases ATP levels, induces neuronal death, and is associated with caspase-3 activation.</p>	<p>*Thiamine-transporter <i>SLC19A3</i>-transfected breast cancer cells show increased apoptosis when exposed to doxorubicin and radiation. The caspase-3-dependent pathway partially causes this increase.</p> <p>*The thiamine deficiency caused by thiamine antagonists leads to caspase-3-induced apoptosis in neuronally differentiated rat PC-12 cells.</p> <p>*Benfotiamine accelerates the healing of ischemic diabetic limbs in mice via the potentiation of angiogenesis and prevents the induction of pro-apoptotic caspase-3.</p> <p>*Subluthiamine, a highly lipid-soluble synthetic analog of thiamine, attenuates trophic factor deprivation-induced cell death in transformed retinal ganglion cells and decreases the expression of cleaved caspase-3.</p>
<p><b>Heme oxygenase-1 (HO-1)</b></p> <p>*Exposure of hepatocellular carcinoma cell lines to Cu<sup>2+</sup> upregulates HO-1 expression.</p> <p>*DL-α-lipoic acid (LA) has an antioxidant effect on copper-induced acute hepatitis in LEC rats. LA treatment significantly suppresses the induction of HO-1.</p>	<p>*Thiamine deficiency produces region-specific neuronal loss and HO-1 induction in microglia.</p> <p>*Thiamine administration blocks further neuronal loss and the induction of HO-1-positive microglia.</p>
<p><b>Apolipoprotein E (ApoE)</b></p> <p>*In women, the <i>ApoE</i> ε4-positive genotype is associated with an earlier onset of Wilson symptoms, particularly among <i>ATP-ase 7B</i> gene <i>p.H1069Q</i> homozygous patients.</p> <p>*The presence of <i>ApoE</i> ε3/3 attenuates clinical manifestations of Wilson's disease in European subjects.</p>	<p>*The frequency of the <i>ApoE</i> ε4 allele is significantly higher in thiamine-deficient dementia patients.</p>

**Table 1:** Genetic Factors Related to Thiamine and Wilson's disease.

increases SERT densities to 98% in Lurcher mice, which is higher than the densities of wild-type mice [73]. Taken together, these findings suggest that thiamine may modulate 5-HT in patients with Wilson's disease.

ROS play a major role in various cell signaling pathways. ROS activate various transcription factors and increase the expression of proteins that control cellular transformation, tumor cell survival, tumor cell proliferation and invasion, angiogenesis, and metastasis [74]. Among metals, copper is the most potent inducer of ROS production and apoptosis. Exposure to copper leads to a time- and dose-dependent increase in ROS generation [29]. ROS accumulation upon exposure to copper in three aquatic hyphomycete species is associated with nuclear morphological alterations, chromatin condensation, caspase-like activity, and DNA strand breaks [75]. When cultured astrocytes and neurons are treated with 20 μM copper, copper causes death (42%) in astrocytes within 48 hours; this effect can be reduced by antioxidants (35-60% less death than in copper-treated cells) [76]. Lipid peroxidation-induced etheno-DNA adducts have been reported in the liver of patients with Wilson's disease [77]. Thus, the etheno adducts have been implicated as initiating DNA damage in copper/iron-induced carcinogenesis in humans. Malondialdehyde levels are higher in children with Wilson's disease than in controls [78]. A decrease of protein thiols, glutathione, and nitrogen species is associated with increased lipid peroxidation in the liver and striatum of LEC rats (a rodent model of Wilson's disease), and total Superoxide-Dismutase (SOD) is consistently increased only in the cortex of LEC rats [46]. Enhanced Mn-SOD immunoreactivity has also been reported

in the dopaminergic neurons of LEC rats [79]. However, oxidative stress has been associated with region-specific neuronal death, and lipid peroxidation products accumulate in the remaining thalamic neurons after 11 days of thiamine deficiency in animal models [80]. *In vitro*, thiamine inhibits lipid peroxidation in rat liver microsomes and free radical oxidation of oleic acid [81]. Thiamine rescues hepatocytes from iron-catalyzed oxidative stress by decreasing lipid peroxidation, mitochondrial and protein damage, and DNA oxidation [82]. Taken together, these findings suggest that thiamine modulates oxidative stress in Wilson's disease.

Nitric Oxide Synthase (NOS) is an enzyme that is involved in the synthesis of Nitric Oxide (NO), which regulates a variety of important physiological responses, including cell migration, the immune response, and apoptosis. Culturing astrocytes and neurons with 20 μM copper causes neuronal death; this neurotoxicity can be prevented by antioxidants and NOS inhibitors [79]. When compared with liver samples from normal controls, 60% of patients with Wilson's disease show a higher expression of inducible NOS in the liver [31], suggesting that NO is a source of increased oxidative stress. The level of NO is higher in children with Wilson's disease compared with healthy children [78,83]. However, increased brain endothelial NOS expression is observed in response to thiamine deficiency [84]. In murine macrophages, benfotiamine also blocks the expression of inducible NOS by lipopolysaccharide-induced cytotoxicity [85]. These findings suggest that thiamine may modulate reactive nitrogen intermediates in patients with Wilson's disease. Table 2 illustrates the role of thiamine in Wilson's disease.

Wilson's disease	Thiamine
<p><b>Serotonin (5-HT)</b></p> <p>*5-HT immunoreactive fiber densities in the cingulate cortex, caudate-putamen, hypothalamus, and hippocampus in Long-Evans Cinnamon rats were significantly higher than the densities of controls at 4, 10, and 20 weeks of age.</p> <p>*The number of aberrant 5-HT immunoreactive fibers in the cingulate cortex, caudate-putamen, hypothalamus, and hippocampus in LEC rats was significantly higher than in controls.</p> <p>*In patients with Wilson's disease, depression is a frequent psychiatric symptom. A prospective study revealed that depressive symptomatology is related to an alteration of presynaptic serotonin transporters.</p> <p>*A significant negative correlation was found between the Hamilton rating scale for depression and SERT density in the thalamus-hypothalamus region in patients with Wilson's disease.</p>	<p>*Serotonergic system dysfunction occurs in thiamine-deficient (TD) mice.</p> <p>*Selective serotonin reuptake inhibitors (SSRIs) significantly inhibits depressive behavior in TD mice.</p> <p>*A significant decrease in 5-HT uptake in synaptosomal preparations of the cerebella of TD rats. Thiamine administration results in a significant reverse of the inhibition of 5-HT uptake.</p>
<p><b>Reactive oxygen Species (ROS)</b></p> <p>*Exposure to copper leads to an increase in ROS generation.</p> <p>*ROS accumulation upon exposure to copper in three aquatic hyphomycete species is associated with the occurrence of nuclear morphological alterations, chromatin condensation, caspase-like activity and DNA strand breaks.</p> <p>*Malondialdehyde levels were higher in Wilson's disease in childhood than in controls.</p> <p>*A decrease of protein-thiols, glutathione and nitrogen species were associated with increased lipid peroxidation in the liver and striatum of Long-Evans Cinnamon (LEC) rats (a rodent model of Wilson's disease), and total superoxide-dismutase (SOD) consistently increased only in the cortex of LEC rats.</p> <p>*Enhanced Mn-SOD immunoreactivity was also reported in the dopaminergic neurons of LEC rats</p>	<p>*Lipid peroxidation product accumulates in the remaining thalamic neurons in TD animal models.</p> <p>*Thiamine inhibits lipid peroxidation and free radical oxidation of oleic acid in rat liver microsomes.</p>
<p><b>Nitric oxide synthetase (NOS)</b></p> <p>*Cultured astrocytes and neurons were treated with 20 μM copper, which caused neuronal death and this neurotoxicity was prevented by antioxidants and NOS inhibitors.</p> <p>*When compared with the liver samples from normal controls, sixty percent of the patients with Wilson's disease showed a higher expression of inducible NOS in the liver.</p> <p>*NO level was higher in children with Wilson's disease compared to healthy children.</p>	<p>*Benfotiamine inhibits iNOS expression in endotoxin-induced uveitis in rats.</p> <p>*Increased brain endothelial NOS expression is observed in cases of thiamine deficiency.</p>

Table 2: Role of thiamine in Wilson's disease.

## Conclusion

The relationship between thiamine and Wilson's disease is discussed. Genetic studies have provided opportunities to determine which proteins may link thiamine to the pathology of Wilson's disease, including gene p53, Bcl-2, caspase-3, HO-1, and ApoE. Thiamine can also act through a number of non-genomic mechanisms, including protein expression, 5-HT, oxidative stress, inflammation, and cellular metabolism. Thiamine supplementation has demonstrated the beneficial role of thiamine in patients with Wilson's disease. Therefore, further investigations on thiamine in Wilson's disease are needed. A more cautious approach would be advisable prior to recommending the widespread use of thiamine in patients with Wilson's disease.

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