American Journal of Psychiatry and Neuroscience
2013; 1(2): 22-37
Published online September 10, 2013 (http://www.sciencepublishinggroup.com/j/ajpn)
doi: 10.11648/j.ajpn.20130102.11

The role of thiamine in autism

Khanh vinh quốc Lương*, Lan Thi Hoàng Nguyễn

Vietnamese American Medical Research Foundation, Westminster, California, U.S.A

Email address:
Lng2687765@aol.com(K. v. q. Lương)

To cite this article:
Khanh vinh quốc Lương, Lan Thi Hoàng Nguyễn. The Role of Thiamine in Autism. *American Journal of Psychiatry and Neuroscience.* Vol. 1, No. 2, 2013, pp. 22-37. doi: 10.11648/j.ajpn.20130102.11

Abstract: Autism spectrum disorders are a group of neuro-developmental conditions characterized by varying degrees of language impairment, including verbal and non-verbal communication, impaired social skill, and repetitive behaviors. In this paper, we review the evidence for an association between autism and thiamine. A relationship between thiamine status and the development of autism has been established, with thiamine supplementation exhibiting a beneficial clinical effect on children with autism. Thiamine may involve in autism via apoptotic factors (transcription factor p53, Bcl-2, and caspase-3), neurotransmitter systems (serotonin, acetylcholine, and glutamate), and oxidative stress (prostaglandins, cyclooxygenase-2, reactive oxygen species, nitric oxide synthase, the reduced form of nicotinamide adenine dinucleotide phosphate, and mitochondrial dysfunction). In addition, thiamine has also been implicated in autism via its effects on basic myelin protein, glycogen synthetase kinase-3β, alpha-1 antitrypsin, and glyoxalase 1. Thiamine may play a role in children with autism. Additional investigation of thiamine in children with autism is needed.

Keywords: Thiamine, Autism, Vitamin B1, Transketolase

1. Introduction

Autism is a childhood-onset neuro-developmental disorder characterized by disturbances in social interactions, imaginative activities, communication, and speech. There is a relationship between thiamine status and autism. There is evidence from animal studies that the developing brain is influenced by a reduced thiamine intake. A correlation exists between the severity of this neuropsychiatric disorder and the degree of alcohol exposure in utero [1]. Alcohol consumption during pregnancy has long-lasting adverse effects that cause structural, behavioral and cognitive damage despite a radical improved in environmental factors [2]. Ethanol impairs the intestinal absorption of thiamine in humans [3-4] and causes thiamine deficiencies in alcoholics. In addition, a woman who consumed herbal remedies containing thiaminase, an enzyme causes thiamine deficiency, during pregnancy gave birth to a girl with autism spectrum disorder (ASD) [5]. It has been suggested that autistic children may relate to inadequate vitamin intake, especially thiamine. States with the highest women, infant, and children (WIC) program have significantly lower rates of autism than those without [6], suggesting that nutritional epidemiology and ecologic study link the possible cause of autism to nutrition. WIC program is known as the Special Supplement Nutrition Program for low-income families. There is also an association has been found between the increase in childhood autism rates and exclusive breast-feeding [6]. Infants who were breast-fed without supplementation had diets that contained less thiamine, riboflavin, and vitamin D than the minimal daily recommendations. Bell and Stewart [7] demonstrated that the developing brain is vulnerable to reduced thiamine intake and that the period of vulnerability may be different for activity and avoidance learning. These authors found that rat pups suckling from thiamine-deficient (TD) dams exhibited of memory deficits. In another study, 21% of children with ASD had a thiamine pyrophosphate (TPP) uptake effect in the TD range [8]. Erythrocyte transketolase stimulation test was abnormal in ASD patients [9-11]. An Israeli study demonstrated the impact of TD during early infancy on aspects of language at 5-7 years of age [12]. The children exposed to TD milk during their first year of life and developed in a high rate of problem with receptive and expressive language. In TD animal studies, rat pulps developed permanent learning and memory deficits as well as aggressive behavior [13-14]. Other studies have shown that TD during brain development provokes neuronal cell loss that persists into adulthood [15]. Thiamine may also have an influence at later stages. Harrell [16] demonstrated that orphan children received thiamine daily for a year were more intelligent, had better visual acuity, faster reaction

time and better memory than control groups. In addition, mice treated with thiamine tetrahydrofurfuryl disulfide (TTFD) showed decreased locomotor activity in solitary open-field testing. During social interaction, the TTFD-treated mice engaged in more passive cuddling-type behaviors than vigorous play-type behavior and showed a decreased startle response to loud noises [17]. Based on the Autism Treatment Evaluation Checklist (ATEC), Lansdale et al. [18] demonstrated that TTFD had a beneficial clinical effect on 8 of 10 children with autism in four areas: communication, sociability, sensory/cognitive awareness, and behavior. These findings suggested that there is a relationship between thiamine and autism. Therefore, we review the role of thiamine in autism in the present paper.

2. The role of Thiamine in Autism

2.1. Apoptotic Factors

The p53 gene and protein play critical roles in the regulation of the normal cell cycle, cell cycle arrest, and apoptotic response. p53 is a transcription factor that plays a major role in determining cell fates in response to DNA damage. The function of p53 is to serve as a critical regulator of neuronal apoptosis in the central nervous system (CNS) [119]. Deranged apoptotic regulation has been reported in children with autism. The size of Purkinje cell decreased by 24% in the brains of children of autism compared with controls [20], suggesting that the Purkinje cell atrophy in autism may have a significant neurohistological heterogeneity among individuals diagnosed with this disorder. p53 values increased by 130% over those in the postmortem parietal cortex blocks of patients with autism [21]. In another report, p53 levels increased by 67.5% and 38% in the superior frontal and cerebellar cortices of patients with autism, respectively [22].Sheikh et al. [23] found an increased p53 expression in the Purkinje and granule cells of the cerebella in people with autism compared with age-matched controls. These findings suggest that deranged apoptotic mechanisms involved in the pathogenesis of patients with autism. In contrast, an increased number of thiamine transporters have been found in cells that over-express thiamine transport genes (mTHTR-1) and in those exposed to conditions that induce DNA damage or p53 activation [24]. Thiamine diphosphate (TDP) inhibits p53 binding, and thiamine inhibits intracellular p53 activity [25]. The expression of p53 decreases significantly in the cultured retinal neurons of diabetic rats treated with thiamine [26]. These observations suggested that the transcription factor p53 is activated in autism with increasing apoptotic response from cellular damage and thiamine ameliorated these effects on cells.

Bcl-2 is a membrane-bound protein that plays a neuro-protective role in the CNS. Bcl-2 inhibits apoptosis and enhances the survival of newborn neurons in the normal and ischemic hippocampus[27]. Bcl-2 mRNA and protein expression are developmentally regulated in both the human and murine brain [28-29]. 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, in some cases, free-radical-induced damage [30]. Bcl-2 has significant neurotropic functions that contribute to normal neuronal growth and the axodendritic branching of neurons. The total Purkinje cell counts were significantly lower in the cerebellar hemispheres and vermises of subject with autism compared control subjects [31]. Abnormalities in the neuronal apoptotic pathways may play a significant role in the pathogenesis of autism. Reduced in Bcl-2 has been reported in the cerebella of subjects with autism [22,32]. A quantification of Bcl-2 levels revealed a 34% to 51% reduction in the people with autism compared with controls [33]. Bcl-2 protein expression was also significantly decreased in the lymphoblasts of people with autism compared with controls [34]. In addition, the global methylation profiling of lymphoblastic cell lines reveals the decreased expression of Bcl-2 proteins in the brains of people with autism [35]. Therefore, the decreased Bcl-2 protein level suggests an increased apoptosis in people with autism. However, B vitamins pre-treatment (B_1, B_6, and B_{12}) had a protective effect in experimentally induced epilepsy of the mouse brain with an early induction of Bcl-2 expression within 12 hours [36]. Thiamine deprivation increased cell death and reduced Bcl-2 expression during hybridoma cell culture [37]. Benfotiamine is a transketolase activator that directs glucose to the pentose phosphate pathway and improves the functional recovery of an infarcted heart with increases in Bcl-2 protein levels [38]. When human and bovine pericytes were intermittently exposed to high glucose, there was a 50-60% decrease in the Bcl-2 to Bax ratio for both expression and concentration; the addition of thiamine and benfotiamine completely reversed this damaging effect [39]. Taken together, thiamine may have a neuro-protective role in autism by increasing apoptotic inhibitor Bcl-2.

Caspases are cysteinyl aspartate-specific proteases that play a critical role in the regulatory and execution phases of apoptosis [40]. Neonatal exposure to sevoflurane, an anesthetic, significantly increased the number of apoptotic cells and increased cleaved caspase-3 in the brain;it also induced abnormal social behaviors and deficits in mouse fear conditioning [41]. Caspase-3 increased in the cerebella of participants with autism [42]. The expression of caspases also increased in the peripheral blood mononuclear cells of patients with ASD [43]. These results suggest that down-regulation of the anti-apoptotic signaling pathway in the autistic brain could be one of the underlying mechanisms responsible for the pathogenesis of autism. Thiamine transporter *SLC19A3* gene-transfected breast cancer cells showed an increase in apoptosis when exposed to doxorubicin and radiation, and the caspase-3-dependent pathway partially mediated this effect [44]. The thiamine deficiency caused by thiamine antagonists leads to caspase-

3 apoptosis in the neuronal differentiated PC-12 cells of rats [45]. Benfotiamine accelerates ischemic diabetic limbs healing in mice via the potentiation of angiogenesis and prevention the induction of pro-apoptotic caspase-3 [46]. Sulbutiamine, a highly lipid-soluble synthetic analog of thiamine, attenuates trophic factor deprivation-induced cell death to transformed retinal ganglion cells (RGC-5) and decreases the expression of cleaved caspase-3 [47]. These findings suggest that thiamine may have a role in autism by inhibiting the apoptotic factor caspase-3 activity.

The role thiamine in anti-apoptosis in autism is summarized in Table 1.

Table 1*: The role of thiamine in anti-apoptosis in Autism.*

Autism	Thiamine
p53 gene *p53 values increased by 130% over control values in the postmortem parietal cortex blocks of patients with autism. * p53 levels increased by 67.5% and 38% in the superior frontal and cerebellar cortices, respectively, of people with autism. *An increased p53 expression in the cerebella Purkinje and granule cells of the brains of people with autism compared with age-matched controls.	* Increased thiamine transporter activities have been found in cells that over-express the genes that code for *thiamine transporters* (*mTHTR-1*) and under conditions of DNA damage or p53 activation. *TDP inhibits p53 binding and thiamine has been inhibits intracellular p53 activity. *The expression of p53 decreases significantly in the cultured retinal neurons of diabetic rats treated with thiamine.
Bcl-2 *Abnormalities in the neuronal apoptotic pathways may play a significant role in the pathogenesis of autism. Reduced Bcl-2 has been reported in the cerebellum of cerebellum of participants with autism. *A quantification of the Bcl-2 levels showed a 34% to 51% reduction in the cerebella of people with autism compared with controls. *Bcl-2 protein expression also decreased significantly in lymphoblasts of people with autism compared with controls. *The global methylation profiling of lymphoblastoid cell lines revealed a decreased expression of Bcl-2 proteins in the brains of the people with autism.	*Vitamin B pre-treatment (B_1, B_6, and B_{12}) had a protective effect on experimental epilepsy in the brains of mouse with an early induction of Bcl-2 expression within 12 hours. *Thiamine deprivation increased cell death and reduced Bcl-2 expression during a hybridoma cell culture. *Benfotiamine improved the functional recovery of infarcted hearts with increased Bcl-2 protein levels. *The Bcl-2 to Bax ratio decreased by 50%-60% (for both expression and concentration) in the human and bovine pericytes intermittently exposed to high glucose; the addition of thiamine and benfotiamine completely reversed this damaging effect.
Caspases *Neonatal exposure to sevoflurane, an anesthetic, significantly increased the number of apoptotic cells and increased cleaved caspase-3 in the brain. This exposure induced abnormal social behaviors and deficits in the fear conditioning of mice. *Caspase-3 increased in the cerebella of participants with autism. *The expression of caspases also increased in the peripheral blood mononuclear cells of patients with autism spectrum disorder (ASD).	*Thiamine-transporter *SLC19A3* gene-transfected breast cancer cells showed an increase in apoptosis when exposed to doxorubicin and radiation. The caspase-3-dependent pathway partially this increases. *The thiamine deficiency caused by thiamine antagonists leads to caspase-3 apoptosis in the neuronal differentiated PC-12 cells of rats. *Benfotiamine accelerates the healing of ischemic diabetic limbs in mice via the potentiation of angiogenesis and prevention the induction of pro-apoptotic caspase-3. *Sulbutiamine, a highly lipid-soluble synthetic analog of thiamine, attenuates trophic factor deprivation induced cell death to transformed retinal ganglion cells (RGC-5) and decreases the expression of cleaved caspase-3.

ASD, autism spectrum disorder; mTHTR-1, thiamine transport genes; TDP, thiamine diphosphate

2.2. Neurotransmitter System

Serotonin (5-HT)is an indolamine 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. 5-HT plays a role in the expression of autism. Acute tryptophan depletion worsens autistic symptoms [48] and some patients with autism respond positively to selective 5-HT re-uptake inhibitors (SSRIs), especially with regard to obsessive-compulsive symptoms [49]. Positron emission tomography (PET) revealed the altered serotonin synthesis in the dentato-thalamo-cortical pathways in boys with autism [50]. Children with autism had high 5-HT levels in their platelets and bloods [51-52]. The number of 5-HT axons increased in both the pathways and terminal regions of the postmortem cortices of young donors who had autism [53]. An animal study suggested that hyper-serotonemia reduces the drive for social attachment by inhibiting separation distress [54]. Another study failed to show the inverse relationship between blood 5-HT and expressive verbal ability [55]. However, McBride et al. [56] examined the effects of autism, race, and puberty with regard to the platelet 5-HT levels of children with autism and mental retardation. These authors suggested that hyper-serotoninemia is more prevalent in children with autism than those without. The *SLC6A4* gene encoded by the 5-HTtransporter (SERT) and plays a prominent role in 5-HT homeostasis. An increased density in the platelet 5-HT transporter was also found in patients with autism [57]. Several gene variants that may change the structure or function of the transporter protein are associated with autism. Variation within genes on the serotonin pathway, particularly *HTR3A* located on chromosome 11, were demonstrated modest effects on autism risk [58]. People with autism in France, Germany, Israel, Portugal, and the

United States exhibited a preferential inheritance of SERT length polymorphism *L* variants [59]. Although the *S* allele is more frequent in Japanese and Irish people with autism [60-61] the *S/S* genotype is significantly associated with all South African ethnic populations with autism [59]. However, SERT polymorphisms are not associated with autism in Brazil or China [62-63]. Recently, transgenic mice have been found to express the *SERT* variant that causes hyper-serotoninemia, 5-HT receptor hypersensitivity, social impairment and repetitive behavior [64]. In addition, serotonergic systems dysfunction occurs in TD diet fed mice; specifically, a marked loss of [^{3}H]5-HT, which labels the indolaminergic fiber systems of the cerebellum, medulla, mid-brain and diencephalon, was found [65]. The SSRI fluvoxamine significantly inhibited depressive behavior in TD mice as measured by an increase of immobility time in a forced swimming test [66]. Patients with low cerebrospinal fluid thiamine concentrations exhibited low 5-hydroxyindoleacetic acid (5-HIAA) values; however, thiamine treatment increased 5-HIAA markedly [67]. There was a significant decrease in the 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 coincide with a dramatic clinical improvement [68]. A pyrithiamine-induced TD-rats increase in the endogenous 5-HIAA of the medulla-pons region occurred simultaneously with the onset of neurological signs; thiamine administration reversed both trends [69]. In addition, thiamine (1-3000 μM) reduced ^{3}H-5-HT uptake to 83% of the controls in human placental choriocarcinoma cells. These cells are the only cell line of human origin expressed in the 5-HT transporter [70]. Lurcher mutant 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 increased SERT densities to 98% in Lurcher mutant mice, which is higher than those of wild-type mice [71].

Regions throughout the neo-cortex receive cholinergic inputs from the basal forebrain. The cholinergic system plays a role in the development and function of cognitive abilities. A disruption in this process may be linked to the cognitive deficits that often accompany autism. Neuronal nicotinic receptors decreased in cerebral and cerebellar cortices of patients with autism, with 65%-73% receptors in the autistic group than in the normal subjects [72]. The nicotinic receptor binding was significantly reduced by 40%-50% in the granule cells, Purkinje cells and molecular layers in the autistic group compared with the normal group [73]. Reduced gene expression of the *α4β2 nicotinic receptor* in the cerebral cortex is a major feature of the neurochemical pathology of autism [74]. Cholinesterase inhibitors decreased irritability and hyperactivity [75], and improved expressive speech and overall behavior over baseline in people with autism [76]. These findings suggest that neuropathologic and neurochemical abnormalities of the cholinergic pathways were implicated in pathogenesis of autism. In addition, TD encephalopathy might involve impairment in cholinergic neurotransmitter function. Thiamine is a coenzyme required to synthesize acetylcholine (ACh). The synthesis of ACh is impaired in the brains of TD rats [77], which leads to a significant reduction in neuronal ACh levels [78]. Animal studies also suggest that thiamine is involved in the presynaptic release of ACh; thiamine binds to nicotinic receptors and exhibits anticholinesterase activity [79]. In addition, thiamine deficiency induces an early central muscarinic cholinergic lesion [80]. Taken together, thiamine may have a role in autism by involving in the cholinergic system.

Glutamate is synthesized from glucose and glutamine in the presynaptic neuronal terminals and serves as a major excitatory neurotransmitter in the CNS. The capacity for cognition and memory is derived from the various input and output pathways between the hippocampus and neo-cortex that rely on glutamatergic signaling [81]. Some studies have found cellular development abnormalities in the limbic system and the postmortem cerebella of people with autism [82-83]. These areas are normally enriched with glutamate receptors. Glutamic acid decarboxylase (GAD) was reduced by 48%-61% in the parietal and cerebellar areas of the brains of people with autism compared with controls [84]. Increased glutamate concentration was demonstrated in the auditory cortex of persons with autism and first-degree relatives [85]. Proton magnetic resonance spectroscopy revealed lower N-acetylaspartate/creatine (NAA/Cr), γ-aminobutyric acid/creatine (GABA/Cr) and glutamate/creatine (Glx/Cr) in the frontal lobes of an autistic group compared with normal controls [86]. *Glutamateδ-1 receptor* knockout mice (*GluD1* KO) were hyperactive and manifested fewer anxiety and depression-like behaviors in a forced swim test as well as robust aggression in the resident-intruder test [87]. Antibodies against glutamic acid decarboxylase 65 (GAD65) have been detected in the serum of patients with autism or ASD [88]. Mitochondrial aspartate/glutamate carrier *SLC25A12* polymorphisms are strongly associated with autism [89-90], and thiamine deficiency results in the down-regulation of glutamate transporters in cultured astrocytes [91]. TD diminishes thiamine-dependent enzymes throughout the brain, but produces a time-dependent selective neuronal loss, glial activation, inflammation, abnormalities in oxidative metabolism and clusters of degenerating neurites in only specific thalamic regions. Furthermore, levels of EAAT-1 and EAAT-2 are diminished by 62% and 71%, respectively, in participant with TD encephalopathy [92]. An N-acetylcysteine treatment prevented the down-regulation of EAAT-2 in the medial thalamus and ameliorated the loss of several other astrocytic proteins. In addition, treatment with pyrithiamine, a central thiamine antagonist, decreased the protein levels of astrocytic glutamate transporters in the medial thalamus [93]. Taken together, thiamine may involve in the autism by modulating neurotransmitters in the brain.

The role thiamine in neurotransmitter system in autism is summarized in Table 2.

2.3. Oxidative Stress

Prostaglandins (PGs) play a role in inflammatory processes. Cyclooxygenase (COX) participates in the conversion of arachidonic acid into PGs. These released prostanoids play an important role in normal neural function, including spatial learning, synaptic plasticity and long-term potentiation [94]. The PGE_2 signaling pathway may have an important role in early development; the expression of four EP (E-prostanoid) receptor' transcripts (EP_1, EP_2, $EP_3\beta$, and EP_4) significantly increases in mouse embryosfrom day 11-15 [95]. The normal laminar pattern of COX-2- in the human cortex is altered in patients with Rett syndrome, a type of ASD [96]. There is an association between the *PTGS2* polymorphism (the gene that encodes COX-2 enzyme) and Korean trios with ASD [97]. These findings suggest that PG pathway may participate in the pathogenesis of autism. In addition, the expressions of COX-2 mRNA and PGE_2 selectively increased in vulnerable regions during the symptomatic stages of TD encephalopathy animal models. Administration of nimesulide, a highly specific COX-2 inhibitor, significantly reduced PGE_2 levels in vulnerable regions [98]. Similarly, benfotiamine inhibits the expression of COX-2 in endotoxin-induced uveitisin rats [99]. Benfotiamine also blocked the expression of COX-2 and its product PGE_2 in murine macrophages via LPS-induced cytotoxicity [100]. These findings suggested that thiamine may play a role in modulating the inflammatory process in autism.

Reactive oxygen species (ROS) play a major role in various cell-signaling pathways. ROS activates various transcription factors and increases in the expression of proteins that control cellular transformation, tumor cell survival, tumor cell proliferation and invasion, angiogenesis, and metastasis. Lipid peroxidation is a chain reaction between polyunsaturated fatty acids and ROS, and it produces both lipid peroxides and hydrocarbon polymers, which are highly toxic to the cell. Malonyldialdehyde (MDA) is an end product of the peroxidation of polyunsaturated fatty acids. Lipid peroxidation elevated in people with autism. The plasma MDA is significantly higher in those with autism than in their siblings without autism [101]. Higher serum MDA and 8-hydroxy-2-deoxyguanosine (8OHdG) levels were found in children with autism compared with controls [102]. 8OHdD levels were also increased in the cerebellum of patients with autism [103-104]. The F_2-isoprostane 8-iso-prostaglandin $F_2\alpha$ is enhanced in children with autism [105]. This isoprostane is a product of nonenzymatic oxidation of arachidonic acid and suggested as a marker of lipid peroxidation. Compared with controls, children with autism had significantly higher urinary levels of isoprostane $F_2\alpha$-VI (2,3-dinor-thromboxane B_2, a marker of lipid peroxidation) and 6-keto-prostaglandin $F_1\alpha$ [106]. Children with autism had higher mitochondrial rates of hydrogen peroxide production compared with controls [107]. The erythrocyte superoxide dismutase (SOD) activity in children with autism was significantly lower than that in normal controls [108]. The glutathione (GSH) plays an important role in a several cellular process including cell differentiation, proliferation, and apoptosis. GSH content was significantly lower in patients with autism compared with the control group [103, 109-111]. In addition, *GSH* pathway gene variations are associated with ASD [112-114]. In the systematic review and meta-analyses, the ASD patients showed decreased blood levels of reduced GSH (27%), GSH peroxidase (GSH-Px) (18%), and increased concentrations of oxidized GSH (45%) relative to controls, whereas SOD, homocysteine, and cystathionine showed no association with ASDs [115]. These findings suggested that oxidative stress participated in the pathogenesis of autism. Similarly, oxidative stress is associated with region-specific neuronal death, and lipid peroxidation product accumulates in the remaining thalamic neurons after 11 days inTD animal models [116]. *In vitro,*thiamine inhibits lipid peroxidation and the free radical oxidation of oleic acid in rat liver microsomes [117]. Male Wistar rats were intoxicated with an ethanol dose; the MDA, reduction GSH and vitamin E values were used as parameters of the liver's antioxidant system and showed improvement for the thiamine-treated group [118]. Thiamine improved the reduced GSH level in acutely alcoholized rats [118]. Taken together, these findings suggested that thiamine modulates oxidative stress in autism.

Nitric oxide synthase (NOS) is an enzyme involved in the synthesis of nitric oxide (NO) and regulates a variety of important physiological responses including cell migration, immune response, and apoptosis. NO affects the development and function of the CNS. NO enhances the release of dopamine in the striatum in animal models [119]. Extracellular dopamine increased following the intrastriatal infusion of NOS substrate [120]. Increased RBC NO levels and plasma GSH-Px were detected in people with autism [121]. A significant elevation level of NO was observed in the plasma of Omani autistic children as compared to their age-matched controls [111]. Decreased levels of enzymatic and non-enzymatic antioxidants and increased concentration of thiobarbituric acid reactive substances (TBARS) and NO were also observed in the blood of autistic children [122]. Lower protein content and higher percentage of nitration in hair and nail of autistic children correlated with their degrees of severity [122]. In a family-based association study, there was a significant but weak evidence for an association between *NOS-IIA* polymorphism and ASD in the Korean population [123]. These findings indicate a possible role of increased oxidative stress and altered enzymatic antioxidants may be relevant to the pathophysiology of autism. Benfotiamine inhibits the expression of iNOS in endotoxin-induced uveitis in rats [101]. Benfotiamine also blocks the expression of iNOS via LPS-induced cytotoxicity in murine macrophages [99]. These findings suggested thiamine may

module reactive nitrogen intermediates in the autism.

The mitochondrial dysfunction and altered energy may influence the social and cognitive deficits in autism [124-125]. Giulivi et al. [108] reported a low pyruvate dehydrogenase (PDH) activity in children with autism. Genetic defects in *pyruvate dehydrogenase complex* (PDHC) are known to cause lactic acidosis, neurological deficits, and premature death [26]. Patients with these defects show reduced activity of PDHC and PDH $E_1\alpha$ subunit and decreased affinity of PDHC for TPP [127-128]. Thiamine treatment is very effective in some PDHC-deficient patients [128-129]. Thiamine regulates the expression of enzymes that require thiamine as a cofactor and thiamine deficiency has been shown to reduce the mRNA levels of transketolase and PDH [130]. In the neuronal metabolism of glucose, TDP is an essential coenzyme for mitochondrial PDH, α-ketoglutarate dehydrogenases complexes, and cytosolic transketolase [131-132]. In thiamine deficiency, the levels of thiamine-dependent and non-thiamine-dependent enzymes (succinate and malate dehydrogenase) in the tricarboxylic cycle are reduced in the mouse brain [133].

The reduced form of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) enzyme complex mediates critical physiological and pathological processes including cell signaling, inflammation and mitogenesis, by generating reactive oxygen species (ROS) from molecular oxygen. Mitochondrial dysfunction and altered energy metabolism might influence the social and cognitive deficits present in people with autism. The NOX activity in the lymphocytic mitochondria of children with autism was significantly lower than in controls [107]. Lower levels of plasma ATP and red blood cell NADH were reported in children with autism than in controls. Vitamin and minerals supplements were associated with greater significant improvement in ATP and NADH levels as well as subscores on the hyperactivity, tantrum, and receptive language in the autism group compared with the placebo group [134-135]. In addition, gene variants of the *NADH-ubiquinone oxidoreductase 1α subcomplex 5* (*NDUFA5*), an enzyme complex in the mitochondrial electron transport chain, are associated with autism [136]. These findings suggest that NOX has a role in autism pathology. Thiamin is an essential coenzyme for transketolase, which is part of the pentose phosphate pathway that helps maintain cellular NADPH levels. In a study of hepatocytes with glyoxal toxicity, thiamin was cytoprotective and restored NADPH levels, glyoxal detoxification and mitochondrial membrane potential [137]. NADPH cytochrome c-reductase levels were increased in TD animals [138]. Benfotiamine treatments under both normo- and hyper-glycemic conditions significantly down-regulated Nox4 expression [139]. In addition, animals fed a high-thiamine diet had approximately 57% of the NADPH-cytochrome c reductase activity of those fed a TD diet [140]. Taken together, thiamine may involve in protecting autism by regulating NADPH-cytochrome c activity.

The role thiamine in oxidative stress in autism is summarized in Table 3.

***Table 3**: Role of thiamine in oxidative stress in autism.*

Autism	Thiamine
Prostaglandins (PGs)	
*The normal laminar pattern of cyclooxygenase-2 (COX-2) in the human cortex is altered in patients with Rett syndrome, a type of ASD. *PTGS2, gene encoded for COX-2, polymorphism is associated with Korean trios with ASD.	*The expression of COX-2 and PGE_2 selectively increased in vulnerable regions of TD encephalopathy animal models. *Benfotiamine inhibits the COX-2 expression and it product PGE_2 in murine macrophages.
Reactive oxygen Species (ROS)	
*Lipid peroxidation elevated in people with autism. *Plasma malonyldialdehyde (MDA) is significantly high in patients with autism. *The F_2-isoprostane 8-iso-prostaglandin F2α is enhanced in children with autism. *The erythrocyte superoxide dismutase (SOD) activity decreases in children with autism.	*Lipid peroxidation product is accumulated in the remaining thalamic neurons in TH animal models. *Thiamine inhibits lipid peroxidation and free radical oxidation of oleic acid in rat liver microsomes.
Nitric oxide synthetase (NOS)	
*Increased erythrocyte nitric oxide (NO) levels and plasma glutathione peroxidase (GSH-Px) were detected in people with autism. *GSH plasma levels were decreased in children with autism. GSH pathway gene variants are associated with ASD.	*Benfotiamine inhibits iNOS expression in endotoxin-induced uveitis in rats. *Thiamine improved the reduced GSH level in acutely alcoholized rats.
NADPH	
*The NOX activity in the lymphocytic mitochondria of children with autism was significantly reduced compared with controls. *Lower levels of plasma ATP and red blood cell NADH were reported in children with autism than in controls. *Vitamin and minerals supplements led to significantly improvement in ATP and NADH as well as on the hyperactivity, tantrum, and receptive language subscores in the autism group compared with placebo group. *Gene variants of the NADH-ubiquinone oxidoreductase 1 alpha subcomplex 5 (NDUFA5), an enzyme complex in the mitochondrial electron transport chain, are associated with autism.	*Thiamin is an essential coenzyme for transketolase, which is a part of the pentose phosphate pathway that helps maintain cellular NADPH levels. In a study of hepatocytes with glyoxal toxicity, thiamin was cytoprotective and restored NADPH levels, glyoxal detoxification and mitochondrial membrane potential. *NADPH cytochrome c-reductase levels increased in thiamine-deficient (TD) animals. *Benfotiamine treatment significantly down-regulated Nox4 expression under both normo- and hyper-glycemic conditions. *Animals fed a high-thiamine diet had approximately 57% of the

Autism	Thiamine
	NADPH-cytochrome c reductase activity of those fed a TD diet.
	*Patients with genetic defects in PDHC show reduced activity of PDHC and PDH (E1)α subunit and decreased affinity of PDHC for thiamine pyrophosphate (TPP).
Pyruvate dehydrogenase (PDH)	*Thiamine treatment is very effective in some PDHC-deficient patients.
*A low pyruvate dehydrogenase (PDH) activity was reported in children with autism.	*Thiamine regulates the expression of enzymes that require thiamine as a cofactor and thiamine deficiency has been shown to reduce the mRNA levels of transketolaseand PDH.
*Genetic defects in in pyruvate dehydrogenase complex (PDHC) are known to cause lactic acidosis, neurological deficits, and premature death.	*Thiamine diphosphate (TDP) is an essential coenzyme for mitochondrial PDH, α-ketoglutarate dehydrogenases complexes, and cytosolic transketolase.
	*In thiamine deficiency, the levels of thiamine-dependent and non-thiamine-dependent enzymes (succinate and malate dehydrogenase) in the tricarboxylic cycle are reduced in the mouse brain.

ASD, autism spectrum disorder; COX, cyclooxygenase; GSH, glutathione; GSH-Px, GSH peroxidase; MDA, malonyldialdehyde; NADPH, nicotinamide adenine dinucleotide phosphate; NOX, NADPH oxidase; NOS, nitric oxide synthase; PDH, pyruvate dehydrogenase; PDHC, pyruvate dehydrogenase complex; PGs, prostaglandins; ROS, reactive oxygen species; SOD, superoxide dismutase; TD, thiamine-deficient; TDP, thiamine diphosphate.

***Table 2**: The role of thiamine in neurotransmitter system in autism.*

Autism	Thiamine
Serotonin (5-HT)	
*Acute tryptophan depletion worsens autistic symptoms and patients with autism may respond to selective 5-HT re-uptake inhibitors (SSRTs).	
*PET revealed the altered serotonin synthesis in the dento-thalamo-cortical pathways in boys with autism.	*Serotonergic system dysfunction occurs in thiamine-deficient mice (TD).
*The 5-HT axons increased postmortem cortices of young donors with autism.	*SSRT significantly inhibited depressive behavior in TD mice.
*High platelet and blood 5-HT levels are reported in children with autism.	*A significantly decreased in the 5-HT uptake in the synaptosomal preparations of TD rats cerebella. Thiamine administration resulted in a significantly reverse of the inhibition of 5-HT uptake.
*An increased density in the platelet 5-HT transporter found in patients with autism.	
*Gene encoded by the 5-HT transporter variants are reported in Autism.	
Acetylcholine	
*A neuronal nicotinic receptors decreased in cerebral and cerebellar cortices of patients with autism.	*Thiamine is a coenzyme required to synthesize acetylcholine, which is impaired in the brains of TD rats.
*The nicotinic receptor binding was significantly reduced by 40%-50% in the granule cells, Prukinje cells and molecular layers in the autistic group.	*Thiamine binds to nicotinic receptors and exhibits anticholinesterase activity.
*Reduced gene expression of the α4β2 nicotinic receptor in the cerebral cortex of autism.	*Thiamine deficiency induces an early central muscrarinic cholinergic lesion.
Glutamate	
*Glutamic acid decarboxylase (GAD) was reduced by 48-61% in the parietal and cerebellar areas of autistic brains.	*Thiamine deficiency results in the down-regulation of glutamate transporters. In cultured astrocytes.
*Proton magnetic resonance spectroscopy revealed a decreased glutamate/creatine in the frontal lobes of autistic group.	*Levels of EAAT-1 and EAAT-2 are diminished by 62% and 71%, respectively, in participants with TD encephalopathy.
*Glutamate δ1 receptor$^{-/-}$ mice were hyperactive and manifest fewer anxiety and depressive-like behaviors.	*A central thiamine antagonist, pyrithiamine, decreased the protein levels of astrocytic glutamate transporters in the medial thalamus.
*Mitochondrial aspartate/glutamate carrier SLC25A12 polymorphisms are strongly associated with autism.	

5-HT, serotonin; GAD, glutamic acid decarboxylase; sSSRIs, selective 5-HT re-uptake inhibitors; TD, thiamine-deficient

2.4. Other Role

Immune comorbidities often are reported in subsets of patients with neuro-developmental disorders, including ASD and attention-deficit hyperactivity disorder. A common immunopathology is an increase in serum autoantibodies against neuron-axon filament protein (anti-NAFP), glial fibrillary acidic protein (anti-GFAP) and myelin basic protein (MBP) relative to control patients. Increases in autoantibodies suggest possible deficits in self-tolerance that may contribute to the formation of brain-specific autoantibodies and subsequent effects on the CNS [141-142]. In midline structures including the region of the absent corpus callosum of BTBR mouse model of autistic-like behavior revealed selective changes in neurodevelopmental proteins and adult hippocampal neurogenesis; the myelin markers 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase) and MBP were reduced [143]. A magnetization transfer imaging study of corpus callosum myelination was significantly higher in children with autism than in typically developing children [144], suggesting abnormal myelination of the corpus callosum in autism. Autistic children had significantly higher serum levels of serotonin and anti-MBP auto-antibodies than

healthy children. However, serum serotonin levels had no significant correlations with serum levels of anti-MBP auto-antibodies in autistic patients [145]. Markham et al. [146] demonstrated that the sensitivity of myelination to experience is reduced in adulthood relative to development in both sexes. High serum anti-NBP antibodies were reported in Egyptian autistic children [147]. Antibodies MBP against fetal brain were revealed in sera of mothers with autistic children [148]. Transmission disequilibrium study suggested that an oligodendrocyte and *myelin glycoprotein* gene allele was associated with families with an autistic proband [149]. Similarly, thiamine deficiency is reported in demyelinized disease. Thiaminepyrophosphatase (TPPase) activity was demonstrated by means of cytochemistry and electron microscopy in association with myelinated fibers in the central and peripheral nervous system of the rat [150]. These findings suggest that that TPPase might play in myelinated fibers, including roles in the conduction of nerve impulses or roles in the maintenance of structural configuration of myelin sheaths. Acute axonal polyneuropathy and Wernicke-Korsakoff encephalopathy developed simultaneously in three patients. Their symptoms of neuropathy lessened within two weeks after an intravenous thiamine infusion [151]. These findings suggest that impaired physiological nerve conduction due to thiamine deficiency. In Wernicke's encephalopathy in nonalcoholic patients, neuronal losses were found only in the medial nucleus of the thalamus and inferior olive, myelin staining demonstrated demyelination and gliosis in those areas [152]. Taken together, thiamine may have a role in the pathogenesis of autism by participating in the development of myelin formation.

Glycogen synthetase kinase-3β (GSK3β) is a protein kinase that is involved in many physiological processes (e.g., metabolism, gene expression and apoptosis). GSK3β is pivotal in controlling neuronal polarity within primary embryonic hippocampal neurons [153]. Mice with a fragile X retardation 1 (*Fmr1*) gene deletion are used to model autistic behaviors. The inhibitory serine phosphorylation of GSK3β is lower in the brain regions of *Fmr1* knockout mice than those of wild-type mice [154]. The impaired inhibition regulation of GSK3β in *Fmr1* knockout mice might contribute to some socialization deficits, and lithium treatment can ameliorate certain socialization impairments [154-156]. The expression of mutant *Tph2* in mice results in a marked reduction (~80%) of brain 5-HT production and leads to behavior abnormalities in emotional states. GSK3β activation accompanies this reduction in brain 5-HT levels. The inactivation of GSK3β in *Tph2* knock-out mice, either using pharmacological or genetic approaches, alleviates the aberrant behaviors produced by a 5-HT deficiency [157]. These findings raise the possibility that GSK3 is a fundamental and central component of Fragile X syndrome pathology. Furthermore, the Wnt/β-catenin pathway plays a critical role in the proliferation, differentiation, apoptosis, and cell outgrowth processes of the CNS during embryonic development [158]. The dysregulation of the Wnt pathway may contribute to the pathogenesis of neurodevelopmental disorders such as autism. Sundilac, an inhibitor of the Wnt/β-catenin pathway, decreased activated GSK3β levels and ameliorated repetitive/stereotypic activity as well as the learning, memory, and behavioral abnormalities of rat autism models [159]. Exposure to pyrithiamine, an anti-thiamine compound, also increases β-amyloid protein accumulation and GSK3 activity in the brain [160]. In an animal Alzheimer's disease model, benfotiamine improved cognitive function, reduced amyloid deposition, and suppressed GSK3 activity [161]. These findings suggest that thiamine may have a role in autism by suppressing GSK3 activity.

Alpha-1 antitrypsin (ATT) is the most abundant circulating serine protease inhibitor. ATT deficiency is a genetic condition that increases the risk of developing a variety of diseases. A low serum ATT level occurs in some children with autism [162]. Significantly more family members of people with had lower ATT serum levels than controls; in addition, children with regressive-onset autism had significantly lower ATT levels than controls. These individuals carried the *PiMZ* genotype and had correspondingly low levels of serum ATT [163]. These findings suggest that ATT has a role in autism pathology. In addition, the toxicological properties of furazolidone suggest that there is a relationship among thiamine, autism, and ATT [164]. Furazolidone increases the amount of brain 5-HT, which is high in people with autism, and potentiated the vasopressor action of tyramine in the chicken [165]. Furazolidone also interfered with thiamine activity and potentiated the ATT deficiency in turkeys [165-166]. In Nubian goats, the signs of furazolidone intoxication resembled those of cerebro-cortical necrosis (thiamine deficiency in ruminants), which was ameliorated by the thiamine administration [167]. In addition, furazolidone might induce cardiomyopathy in the turkey and is indistinguishable from spontaneous round heart disease (RHD) [168]. Turkeys with RHD often have a deficiency in ATT and their liver cells are remarkable similar to those of persons with inherited ATT deficiency [169]. It would be useful as a human ATT deficiency model [166]. Moreover, the *ATT* polymorphism with a non-MM genotype significantly increased the incidence of thiamine deficiency. *PiMZ* genotype had significantly increased proportion (46%) of brain MRI T2 white matter abnormalities [170].

Glyoxalase 1 (Glyo-1) catalyzes the first and rate-limiting step of methylglyoxal (MG) removal, which is the major precursor of advanced glycation end product (AGE) formation. Carriers of the *Glyo-1* gene are susceptible to autism, and *Glyo-1* variants are associated with autism [171-172]. These studies also found elevated levels of AGE receptors (RAGEs) and an accumulation of AGE the brains of people with autism. Another study revealed reduced endogenous secretory RAGE plasma levels and elevated concentrations of the pro-inflammatory ligand S100 in

patients with ASD compared with controls [173], which indicates a dysfunction of the AGE-RAGE axis in people with autism. AGE is a heterogeneous group of macromolecules formed by the non-enzymatic glycation of proteins, lipids and nucleic acids. RAGEs are multi-ligand receptors; their ligands are also likely to recognize several receptors in mediating their biological effects [174]. Thiamine and a benfotiamine supplement prevented tissue accumulation and increased the urinary excretion of protein glycation, oxidation and nitration adducts associated with experimental diabetes [175]. Karachalias et al. [176] reported that the hydroimidazolone of AGE residues derived from glyoxal and methylglyoxal (G-H1 and MG-H1, respectively) increased by 115% and 68%, respectively, in streptozotocin-induced diabetic rats, and thiamine and benfotiamine normalized these residues. However, N-carboxymethyl-lysine (CML) and N-carboxyethyl-lysine (CEL) residues increased by 74% and 118%, respectively, in diabetic-induced rats, and only thiamine normalized these residues. Serum markers of endothelial dysfunction, oxidative stress, and AGE increased after a meal high in AGE content. Benfotiamine significantly reduced these effects [177]. The addition of benfotiamine enhanced transketolase activity and decreased the expression of AGE and RAGE in a peritoneal dialysis model of uremic rats [178]. The combined administration of thiamine and vitamin B6 to patients with diabetic nephropathy decreased DNA glycation in leukocytes; however, vitamin B6 alone did not have such an effect [179]. Taken together, thiamine may have a role in autism by modulating on ACE formation.

Other role thiamine in in autism is summarized in Table 4.

Table 4: *Other role of thiamine in autism.*

Autism	Thiamine
Myelin Basic Protein (MBP) *Increased autoantibodies to MBP in Autism.	*TD is reported in demyelinized disease. *Thiamine pyrophosphatase activity was associated with myelinated fibers in the nerves.
Glycogen synthetase kinase-3β (GSK3β) *Mice with the fragile X retardation 1 (*Fmr1*) gene deletion are used to model autistic behaviors. The inhibitory serine phosphorylation of GSK3β is lower in the brain regions of *Fmr1* knockout mice compared with wild-type mice. *The impaired inhibition regulation of GSK3β in *Fmr1* knock-out mice may contribute to some socialization deficits, and lithium treatment can ameliorate certain socialization impairments. *The expression of mutant *Tph2* results in the marked reduction (~80%) of brain serotonin (5-HT) production in mice and leads to behavioral and emotional abnormalities. GSK3β activation accompanies this brain 5-HT levels reduction. *The inactivation of GSK3β in *Tph2* knock-out mice, using either pharmacological or genetic approaches, alleviates the aberrant behaviors produced by a 5-HT deficiency. *Sundilac, an inhibitor of the Wnt/β-catenin pathway, decreased activated GSK3β levels and ameliorated repetitive/stereotypic activities, learning, memory, and behavioral in autistic models of rats.	*Exposure to pyrithiamine, an anti-thiamine compound, also increases β-amyloid protein accumulation and GSK3 activity in the brain. *In an animal Alzheimer's disease model, benfotiamine improved the cognitive function, reduced amyloid deposition, and suppressed GSK3 activity.
Alpha-1 antitrypsin(ATT) * A low serum ATT level was found in some children with autism. *Significantly more family members of children with autism had lower ATT serum levels than controls; in addition, children with regressive-onset autism had significantly lower ATT levels than controls. These individuals carried the Pi MZ genotype and exhibited correspondingly low levels of serum ATT.	*The toxicological properties of furazolidone suggested a relationship among thiamine, autism, and ATT. *Furazolidone increased the amount of brain 5-HT, which is high in people of autism and potentiated the vasopressor action of tyramine in the chicken. *Furazolidone also interfered with the thiamine use in turkey. *In addition, furazolidone may induce cardiomyopathy in a turkey model of human for ATT deficiency. *Moreover, the ATT polymorphism with a non-MM genotype significantly increased the incidence of thiamine deficiency.
Glyoxalase 1 (Glyo-1) *Carriers of the Glyo-1 gene are susceptible to autism. **Glyo-1* variants are associated with Autism. Studies revealed elevated levels AGE receptors (RAGEs) and an accumulation of AGE in the brains of people with autism. *Study revealed reduced endogenous secretory RAGE plasma levels and elevated concentrations of its pro-inflammatory ligand S100 in patients with ASD compared with controls, which indicates the dysfunction of the AGE-RAGE axis in people with autism.	*Thiamine and benfotiamine supplementation prevented tissue accumulation and increased the urinary excretion of protein glycation, oxidation and nitration adducts in experimental diabetes. *The AGE hydroimidazolone residues derived from glyoxal and methylglyoxal (G-H1 and MG-H1) increased by 115% and 68%, respectively, in streptozotocin-induced (STZ) diabetic rats; thiamine and benfotiamine normalized these residues. However, N-carboxymethyl-lysine (CML) and N-carboxyethyl-lysine (CEL) residues increased by 74% and 118%, respectively, in diabetic-induced rats and were normalized by thiamine only. *Serum markers of endothelial dysfunction, oxidative stress, and AGE increased after a meal high in AGE content. Benfotiamine significantly reduced these effects.

Autism	Thiamine
	*In a model of peritoneal dialysis in uremic rats, the addition of benfotiamine led to enhanced transketolase activity and the decreased expression of AGE and RAGE. *The combined administration of thiamine and vitamin B6 to patients with diabetic nephropathy decreased DNA glycation in leukocytes; however, vitamin B6 alone did not have such an effect.

5-HT, serotonin; AGE, advanced glycation end product; anti-GFAP, anti-glial fibrillary acidic protein; anti-NAFP, anti-neuron-axon filament protein; ATT, alpha-1 antitrypsin; Glyo-1, Glyoxalase 1; GSK3β, glycogen synthetase kinase-3β; MBP, myelin basic protein; MDA, malonyldialdehyde; RAGEs, AGE receptors; RHD, TD, thiamine-deficient.

3. Conclusions

The relationship between thiamine and autism is reviewed in the present paper. Thiamine may involve in autism via apoptotic factors, neurotransmitter systems, and oxidative stress. In addition, thiamine has also been implicated in autism via its effects on basic myelin protein, glycogen synthetase kinase-3β, alpha-1 antitrypsin, and glyoxalase 1. Supplements demonstrated the beneficial role of thiamine in people with autism. Therefore, further investigations of thiamine in people with autism are needed, and a cautious approach is advisable before recommending the widespread use of thiamine for patients with autism.

Abbreviations

5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; 8OHdG , 8-hydroxy-2-deoxyguanosine; Ach, acetylcholine; AGE, advanced glycation end product; anti-GFAP, anti-glial fibrillary acidic protein; anti-NAFP, anti-neuron-axon filament protein; ASD, autism spectrum disorder; ATT, alpha-1 antitrypsin; CNS, central nervous system; COX, cyclooxygenase; GAD, glutamic acid decarboxylase; Glyo-1, Glyoxalase 1; GSH, glutathione; GSH-Px, GSH peroxidase; GSK3β, glycogen synthetase kinase-3β; MBP, myelin basic protein; MDA, malonyldialdehyde; MMPI, Minnesota Multiphasic Personality Inventory; m THTR-1, thiamine transport genes; NAA/Cr, N-acetylaspartate/creatine; NADPH, nicotinamide adenine dinucleotide phosphate;NOX, NADPH oxidase; NOS, nitric oxide synthase; PDH, pyruvate dehydrogenase; PDHC, pyruvate dehydrogenase complex; PGs, prostaglandins; RAGEs, AGE receptors; RHD, round heart disease; ROS, reactive oxygen species; SOD, superoxide dismutase; sSSRIs, selective 5-HT re-uptake inhibitors; TBARS, thiobarbituric acid reactive substances; TD, thiamine-deficient; TDP, thiamine diphosphate; TPP, thiamine pyrophosphate; TTPase, thiamine pyrophosphatase; TTFP, thiamine tetrahydrofurfuryl disulfide; WIC, women, infant, and children program.

Acknowledgment

Conflict of interest statement: The authors report no competing interests.

Ethical Approval: Not required

Funding: The authors received no funding for this study.

References

[1] Aronson M, Hagberg B, Gillberg C:Attention deficits and autistic spectrum problems in children exposed to alcohol during gestation: a follow-up study.Dev Med Child Neurol 1997, 39:583-587.

[2] Landgren M, Svensson L, Strömland K, Andersson Grönlund M: Prenatal alcohol exposure and neurodevelopmental disorders in children adopted from eastern Europe. Pediatrics 2010, 125:e1178-1185.

[3] Tomasulo PA, Kater RMH, Iber FL: Impairment of thiamine absorption in alcoholism. Am J Clin Nutr 1968, 21:1340-1344.

[4] Thomson AD, Baker H, Leevy CM: Pattern of 35 S-thiamine hydrochloride absorption in the malnourished alcoholic patient. J Lab Clin Med 1970, 76:34-45.

[5] Ortega García JA, Angulo MG, Sobrino-Najul EJ, Soldin OP, Mira AP, Martínez-Salcedo E, Claudio L: Prenatal exposure of a girl with autism spectrum disorder to 'horsetail' (Equisetum arvense) herbal remedy and alcohol: a case report. J Med Case Reports 2011, 5:129.

[6] Shamberger RJ. Autism rates associated with nutrition and the WIC program. J Am Coll Nutr 2011, 30:348-353.

[7] Bell JM, Stewart CN: Effects of fetal and early postnatal thiamin deficiency on avoidance learning in rats. J Nutr 1979, 109:1577-1583.

[8] Obrenovich ME, Shamberger RJ, Lonsdale D: Altered heavy metals and transketolase found in autistic spectrum disorder. Biol Trace Elem Res 2011, 144:475-486.

[9] Raiten DJ, Massaro T, Zuckerman C: Vitamin and trace element assessment of autistic and learning disabled children. Nutr Behav 1984, 2:9-17.

[10] Obrenovitch ME, Shamberger RJ, Londale D: Altered heavy metals and transketolase found in autistic spectrum disorder. Biol Trace Elem Res 2011, 144:475-486.

[11] Lonsdale D, Shamberger RJ: Red cell transketolase as an indicator of nutritional deficiency. Am J Clin Nutr 1980, 33:205-211.

[12] Fattal-Valevski A, Azouri-Fattal I, Greenstein YJ, Guindy M, Blau A, Zelnik N: Delayed language development due to infantile thiamine deficiency. Dev Med Child Neurol 2009, 51:629-634.

[13] Bâ A: Functional vulnerability of developing central nervous system to maternal thiamine deficiencies in the rat. Dev Psychobiol 2005, 47:408-414.

[14] Terasawa M, Nakahara T, Tsukada N, Sugawara A, Itokawa Y: The relationship between thiamine deficiency and performance of a learning task in rats. Metab Brain Dis 1999, 14:137-148.

[15] Bâ A, N'Douba V, D'Almeida MA, Seri BV: Effects of maternal thiamine deficiencies on the pyramidal and granule cells of the hippocampus of rat pups. Acta Neurobiol Exp (Wars) 2005, 65:387-398.

[16] Harrell RF: Mental response to added thiamine. J Nutr 1946, 31:283-298.

[17] Hills JI, Golub MS, Bettendorff L, Keen CL: The effect of thiamin tetrahydrofurfuryl disulfide on behavior of juvenile DBA/2J mice. Neurotoxicol Teratol 2012, 34:242-252.

[18] Lonsdale D, Shamberger RJ, Audhya T: Treatment of autism spectrum children with thiamine tetrahydrofurfuryl disulfide: a pilot study. Neuro Endocrinol Lett 2002, 23:303-308.

[19] Araki N, Morimasa T, Sakai T, Tokuoh H, Yunoue S, Kamo M, Miyazaki K, Abe K, Saya H, Tsugita A: Comparative analysis of brain proteins from p53-deficient mice by two-dimensional electrophoresis. Electrophoresis 2000, 21:1880-1889.

[20] Fatemi SH, Halt AR, Realmuto G, Earle J, Kist DA, Thuras P, Merz A: Purkinje cell size is reduced in cerebellum of patients with autism. Cell Mol Neurobiol 2002, 22:171-175.

[21] Fatemi SH, Halt AR: Altered levels of Bcl2 and p53 proteins in parietal cortex reflect deranged apoptotic regulation in autism. Synapse 2001, 42:281-284.

[22] Araghi-Niknam M, Fatemi SH: Levels of Bcl-2 and P53 are altered in superior frontal and cerebellar cortices of autistic subjects. Cell Mol Neurobiol 2003, 23:945-952.

[23] Sheikh AM, Malik M, Wen G, Chauhan A, Chauhan V, Gong CX, Liu F, Brown WT, Li X: BDNF-Akt-Bcl2 antiapoptotic signaling pathway is compromised in the brain of autistic subjects. J Neurosci Res 2010, 88:2641-2647.

[24] Lo PK, Chen JY, Tang PP, Lin J, Lin CH, Su LT, Wu CH, Chen TL, Yang Y, Wang FF: Identification of a mouse thiamine transporter gene as a direct transcriptional target for p53. J Biol Chem 2001, 276:37186-37193.

[25] McLure KG, Takagi M, Kastan MB: NAD^+ modulates p53 DNA binding specificity and function. Mol Cellular Biol 2004, 24:9958-9967.

[26] Yang Z, Ge J, Yin W, Shen H, Liu H, Guo Y: The expression of p53, MDM2 and Ref1 gene in cultured retina neurons of SD rats treated with vitamin B1 and/or elevated pressure. Yan Ke Xue Bao 2004, 20:259-263. [Article in Chinese]

[27] Sasaki T, Kitagawa K, Yagita Y, Sugiura S, Omura-Matsuoka E, Tanaka S, Matsushita K, Okano H, Tsujimoto Y, Hori M: Bcl2 enhances survival of newborn neurons in the normal and ischemic hippocampus. J Neurosci Res 2006, 84:1187-1196.

[28] Jarskog LF, Gilmore JH. Developmental expression of Bcl-2 protein in human cortex. Brain Res Dev Brain Res 2000, 119:225-230.

[29] Shimohama S, Fujimoto S, Sumida Y, Tanino H: Differential expression of rat brain bcl-2 family proteins in development and aging. Biochem Biophys Res Commun 1998, 252:92-96.

[30] Zhong LT, Sarafian T, Kane DJ, Charles AC, Mah SP, Edwards RH, Bredesen DE: bcl-2 inhibits death of central neural cells induced by multiple agents. Proc Natl Acad Sci U S A 1993, 90:4533-4537.

[31] Ritvo ER, Freeman BJ, Scheibel AB, Duong T, Robinson H, Guthrie D, Ritvo A: Lower Purkinje cell counts in the cerebella of four autistic subjects: initial findings of the UCLA-NSAC Autopsy Research Report. Am J Psychiatry 1986, 143:862-866.

[32] Ghanizadeh A: Malondialdehyde, Bcl-2, Superoxide Dismutase and Glutathione Peroxidase may Mediate the Association of Sonic Hedgehog Protein and Oxidative Stress in Autism. Neurochem Res 2012, 37:899-901.

[33] Fatemi SH, Stary JM, Halt AR, Realmuto GR: Dysregulation of Reelin and Bcl-2 proteins in autistic cerebellum. J Autism Dev Disord 2001, 31:529-535.

[34] Malik M, Sheikh AM, Wen G, Spivack W, Brown WT, Li X: Expression of inflammatory cytokines, Bcl2 and cathepsin D are altered in lymphoblasts of autistic subjects. Immunobiology 2011, 216:80-85.

[35] Nguyen A, Rauch TA, Pfeifer GP, Hu VW: Global methylation profiling of lymphoblastoid cell lines reveals epigenetic contributions to autism spectrum disorders and a novel autism candidate gene, RORA, whose protein product is reduced in autistic brain. FASEB J 2010, 24:3036-3051.

[36] Rabie T, Mühlhofer W, Bruckner T, Schwab A, Bauer AT, Zimmermann M, Bonke D, Marti HH, Schenkel J: Transient protective effect of B-vitamins in experimental epilepsy in the mouse brain. J Mol Neurosci 2010, 41:74-79.

[37] Ishaque A, Al-Rubeai M: Role of vitamins in determining apoptosis and extent of suppression by bcl-2 during hybridoma cell culture. Apoptosis 2002, 7:231-239.

[38] Katare R, Caporali A, Emanueli C, Madeddu P: Benfotiamine improves functional recovery of the infarcted heart via activation of pro-survival G6PD/Akt signaling pathway and modulation of neurohormonal response. J Mol Cell Cardiol 2010, 49:625-638.

[39] Beltramo E, Berrone E, Tarallo S, Porta M: Different apoptotic responses of human and bovine pericytes to fluctuating glucose levels and protective role of thiamine. Diabetes Metab Res Rev 2009, 25:566-576.

[40] Salvesen GS, Riedl SJ. Caspase mechanisms. Adv Exp Med Biol 2008, 615:13-23.

[41] Satomoto M, Satoh Y, Terui K, Miyao H, Takishima K, Ito M, Imaki J: Neonatal exposure to sevoflurane induces abnormal social behaviors and deficits in fear conditioning in mice. Anesthesiology 2009, 110:628-637.

[42] Sheikh AM, Li X, Wen G, Tauqeer Z, Brown WT, Malik M: Cathepsin D and apoptosis related proteins are elevated in the brain of autistic subjects. Neuroscience 2010, 165:363-370.

[43] Siniscalco D, Sapone A, Giordano C, Cirillo A, de Novellis V, de Magistris L, Rossi F, Fasano A, Maione S, Antonucci N: The Expression of Caspases is Enhanced in Peripheral Blood Mononuclear Cells of Autism Spectrum Disorder Patients. J Autism Dev Disord 2012, 42:1403-1410.

[44] Liu S, Huang H, Lu X, Golinski M, Comesse S, Watt D,

Grossman RB, Moscow JA: Down-regulation of thiamine transporter THTR2 gene expression in breast cancer and its association with resistance to apoptosis. Mol Cancer Res 2003, 1:665-673.

[45] Chornyy S, Parkhomenko J, Chorna N: Thiamine deficiency caused by thiamine antagonists triggers upregulation of apoptosis inducing factor gene expression and leads to caspase 3-mediated apoptosis in neuronally differentiated rat PC-12 cells. Acta Biochim Pol 2007, 54:315-522.

[46] Gadau S, Emanueli C, Van Linthout S, Graiani G, Todaro M, Meloni M, Campesi I, Invernici G, Spillmann F, Ward K, Madeddu P: Benfotiamine accelerates the healing of ischaemic diabetic limbs in mice through protein kinase B/Akt-mediated potentiation of angiogenesis and inhibition of apoptosis. Diabetologia 2006, 49:405-420.

[47] Kang KD, Majid AS, Kim KA, Kang K, Ahn HR, Nho CW, Jung SH: Sulbutiamine counteracts trophic factor deprivation induced apoptotic cell death in transformed retinal ganglion cells. Neurochem Res 2010, 35:1828-1839.

[48] McDougle CJ, Naylor ST, Cohen DJ, Aghajanian GK, Heninger GR, Price LH: Effects of tryptophan depletion in drug-free adults with autistic disorder. Arch Gen Psychiatry 1996, 53:993-1000.

[49] Kolevzon A, Mathewson KA, Hollander E. Selective serotonin reuptake inhibitors in autism: a review of efficacy and tolerability. J Clin Psychiatry 2006, 67:407-414.

[50] Chugani DC, Muzik O, Rothermel R, Behen M, Chakraborty P, Mangner T, da Silva EA, Chugani HT: Altered serotonin synthesis in the dentatothalamocortical pathway in autistic boys. Ann Neurol 1997, 42:666-669.

[51] de Villard R, Flachaire E, Thoulon JM, Dalery J, Maillet J, Chauvin C, Quincy C, Renaud B: Platelet serotonin concentrations in autistic children and members of their families. Encephale 1986, 12:139-142. [Article in French]

[52] Anderson GM, Horne WC, Chatterjee D, Cohen DJ: The hyperserotonemia of autism. Ann N Y Acad Sci 1990, 600:331-340.

[53] Azmitia EC, Singh JS, Whitaker-Azmitia PM: Increased serotonin axons (immunoreactive to 5-HT transporter) in postmortem brains from young autism donors. Neuropharm 2011, 60:1347-1354

[54] Chamberlain RS, Herman BH: A novel biochemical model linking dysfunctions in brain melatonin, proopiomelanocortin peptides, and serotonin in autism. Biol Psych 1990, 28:773-793.

[55] Cuccaro ML, Wright HH, Abramson RK, Marsteller FA, Valentine J: Whole-blood serotonin and cognitive functioning in autistic individuals and their first-degree relatives. Neuropsychiatry Clin Neurosci 1993, 5:94-101.

[56] McBride PA, Anderson GM, Hertzig ME, Snow ME, Thompson SM, Khait VD, Shapiro T, Cohen DJ: Effects of diagnosis, race, and puberty on platelet serotonin levels in autism and mental retardation. J Am Acad Child Adolesc Psych 1998, 37:767-776.

[57] Marazziti D, Muratori F, Cesari A, Masala I, Baroni S, Giannaccini G, Dell'Osso L, Cosenza A, Pfanner P, Cassano GB: Increased density of the platelet serotonin transporter in autism. Pharmacopsychiatry 2000, 33:165-168.

[58] Anderson BM, Schnetz-Boutaud NC, Bartlett J, Wotawa AM, Wright HH, Abramson RK, Cuccaro ML, Gilbert JR, Pericak-Vance MA, Haines JL: Examination of association of genes in the serotonin system to autism. Neurogenetics 2009, 10:209-216.

[59] Arieff Z, Kaur M, Gameeldien H, van der Merwe L, Bajic VB: 5-HTTLPR polymorphism: analysis in South African autistic individuals. Hum Biol 2010, 82:291-300.

[60] Koishi S, Yamamoto K, Matsumoto H, Koishi S, Enseki Y, Oya A, Asakura A, Aoki Y, Atsumi M, Iga T, Inomata J, Inoko H, Sasaki T, Nanba E, Kato N, Ishii T, Yamazaki K: Serotonin transporter gene promoter polymorphism and autism: a family-based genetic association study in Japanese population. Brain Dev 2006, 28:257-260.

[61] Conroy J, Meally E, Kearney G, Fitzgerald M, Gill M, Gallagher L: Serotonin transporter gene and autism: a haplotype analysis in an Irish autistic population. Mol Psych 2004, 9:587-593.

[62] Longo D, Schüler-Faccini L, Brandalize AP, dos Santos Riesgo R, Bau CH: Influence of the 5-HTTLPR polymorphism and environmental risk factors in a Brazilian sample of patients with autism spectrum disorders. Brain Res 2009, 1267:9-17.

[63] Wu S, Guo Y, Jia M, Ruan Y, Shuang M, Liu J, Gong X, Zhang Y, Yang J, Yang X, Zhang D: Lack of evidence for association between the serotonin transporter gene (SLC6A4) polymorphisms and autism in the Chinese trios. Neurosci Lett 2005, 381:1-5.

[64] Veenstra-VanderWeele J, Muller CL, Iwamoto H, Sauer JE, Owens WA, Shah CR, Cohen J, Mannangatti P, Jessen T, Thompson BJ, Ye R, Kerr TM, Carneiro AM, Crawley JN, Sanders-Bush E, McMahon DG, Ramamoorthy S, Daws LC, Sutcliffe JS, Blakely RD: Autism gene variant causes hyperserotonemia, serotonin receptor hypersensitivity, social impairment and repetitive behavior. Proc Natl Acad Sci U S A 2012, 109:5469-5474.

[65] Chan-Palay V, Plaitakis A, Nicklas W, Berl S: Autoradiographic demonstration of loss of labeled indoleamine axons of the cerebellum in chronic diet-induced thiamine deficiency. Brain Res 1977, 138:380-384.

[66] Murata A, Nakagawasai O, Yamadera F, Oba A, Wakui K, Arai Y, Tadano T: Dysfunction of serotonergic systems in thiamine-deficient diet fed mice: effects of SSRI on abnormality induced by thiamine deficiency. Nihon Shinkei Seishin Yakurigaku Zasshi 2004, 24:93-99 [Article in Japanese]

[67] Botez MI, Young SN, Bachevalier J, Gauthier S: Thiamine deficiency and cerebrospinal fluid 5-hydroxyindoleacetic acid: a preliminary study. J Neurol Neurosurg Psychiatry 1982, 45:731-733.

[68] Plaitakis A, Nicklas WJ, Berl S:Thiamine deficiency: selective impairment of the cerebellar serotonergic system. Neurology 1978, 28:691-698.

[69] Van Woert MH, Plaitakis A, Hwang EC, Berl S: Effect of thiamine deficiency on brain serotonin turnover. Brain Res 1979, 179:103-110.

[70] Keating E, Lemos C, Monteiro R, Azevedo I, Martel F: The effect of a series of organic cations upon the plasmalemmal serotonin transporter, SERT.Life Sci 2004, 76:103-119.

[71] Le Marec N, Hébert C, Botez MI, Botez-Marquard T, Marchand L, Reader TA: Serotonin innervation of Lurcher mutant mice: basic data and manipulation with a combination of amantadine, thiamine and L-tryptophan. Brain Res Bull 1999, 48:195-201.

[72] Perry EK, Lee ML, Martin-Ruiz CM, Court JA, Volsen SG, Merrit J, Folly E, Iversen PE, Bauman ML, Perry RH, Wenk GL: Cholinergic activity in autism: abnormalities in the cerebral cortex and basal forebrain. Am J Psychiatry 2001, 158:1058-1066.

[73] Lee M, Martin-Ruiz C, Graham A, Court J, Jaros E, Perry R, Iversen P, Bauman M, Perry E: Nicotinic receptor abnormalities in the cerebellar cortex in autism. Brain 2002, 125:1483-1495.

[74] Martin-Ruiz CM, Lee M, Perry RH, Baumann M, Court JA, Perry EK: Molecular analysis of nicotinic receptor expression in autism. Brain Res Mol Brain Res 2004, 123:81-90.

[75] Hardan AY, Handen BL: A retrospective open trial of adjunctive donepezil in children and adolescents with autistic disorder. J Child Adolesc Psychopharmacol 2002, 12:237-241.

[76] Chez MG, Aimonovitch M, Buchanan T, Mrazek S, Tremb RJ: Treating autistic spectrum disorders in children: utility of the cholinesterase inhibitor rivastigmine tartrate. J Child Neurol 2004, 19:165-169.

[77] Ruenwongsa P, Pattanavibag S: Impairment of acetylcholine synthesis in deficient rats developed by prolonged tea consumption. Life Sci 1984, 34:365-370.

[78] Vorhees CV, Schmidt DE, Barrett RJ: Effects of pyrithiamin on acetylcholine levels and utilization in rat brain. Brain Res Bull 1978, 3:493-496.

[79] Meador KJ, Nichols ME, Franke P, Durkin MW, Oberzan RL, Moore EE, Loring DW: Evidence for a central cholinergic effect of high-dose thiamine. Ann Neurol 1993, 34:724-726.

[80] Barclay LL, Gibson GE, Blass JP: Impairment of behavior and acetylcholine metabolism in thiamine deficiency. J Pharmacol Exp Ther 1981, 217:537-543.

[81] Squire LR, Zola-Morgan S: The medial temporal lobe memory system. Science 1991, 253:1380-1386.

[82] Bauman ML, Kemper TL: Neuroanatomic observations of the brain in autism: a review and future directions. Int J Dev Neurosci 2005, 23:183-187.

[83] Raymond GV, Bauman ML, Kemper TL: Hippocampus in autism: a Golgi analysis.Acta Neuropathol1996, 91:117-119.

[84] Fatemi SH, Halt AR, Stary JM, Kanodia R, Schulz SC, Realmuto GR: Glutamic acid decarboxylase 65 and 67 kDa proteins are reduced in autistic parietal and cerebellar cortices. Biol Psychiatry 2002, 52:805-810.

[85] Brown MS, Singel D, Hepburn S, Rojas DC: Increased Glutamate Concentration in the Auditory Cortex of Persons With Autism and First-Degree Relatives: A (1) H-MRS Study. Autism Res 2013, 6:1-10.

[86] Kubas B, Kułak W, Sobaniec W, Tarasow E, Lebkowska U, Walecki J: Metabolite alterations in autistic children: a 1H MR spectroscopy study. Adv Med Sci 2012, 57:152-156.

[87] Yadav R, Gupta SC, Hillman BG, Bhatt JM, Stairs DJ, Dravid SM: Deletion of glutamate delta-1 receptor in mouse leads to aberrant emotional and social behaviors. PLoS One 2012, 7:e32969.

[88] Rout UK, Mungan NK, Dhossche DM: Presence of GAD65 autoantibodies in the serum of children with autism or ADHD. Eur Child Adolesc Psychiatry 2012, 21:141-147.

[89] Silverman JM, Buxbaum JD, Ramoz N, Schmeidler J, Reichenberg A, Hollander E, Angelo G, Smith CJ, Kryzak LA: Autism-related routines and rituals associated with a mitochondrial aspartate/glutamate carrier SLC25A12 polymorphism. Am J Med Genet B Neuropsychiatr Gene 2008, 147:408-410.

[90] Turunen JA, Rehnström K, Kilpinen H, Kuokkanen M, Kempas E, Ylisaukko-Oja T: Mitochondrial aspartate/glutamate carrier SLC25A12 gene is associated with autism. Autism Res 2008, 1:189-192.

[91] Hazell AS, Pannunzio P, Rama Rao KV, Pow DV, Rambaldi A: Thiamine deficiency results in downregulation of the GLAST glutamate transporter in cultured astrocytes. Glia 2003, 43:175-184.

[92] 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. Neurobiol Aging 2009, 30:1587-1600.

[93] Hazell AS, Rao KV, Danbolt NC, Pow DV, Butterworth RF: Selective down-regulation of the astrocyte glutamate transporters GLT-1 and GLAST within the medial thalamus in experimental Wernicke's encephalopathy. J Neurochem 2001, 78:560-568.

[94] Tassoni D, Kaur G, Weisinger RS, Sinclair AJ: The role of eicosanoids in the brain. Asia Pac J Clin Nutr 2008, 17:220-228.

[95] Tamiji J, Crawford DA: Prostaglandin E_2 and misoprostol induce neurite retraction in Neuro-2a cells. Biochem Biophys Res Commun 2010, 398:450-456.

[96] Kaufmann WE, Worley PF, Taylor CV, Bremer M, Isakson PC: Cyclooxygenase-2 expression during rat neocortical development and in Rett syndrome. Brain Dev 1997, 19:25-34.

[97] Yoo HJ, Cho IH, Park M, Cho E, Cho SC, Kim BN, Kim JW, Kim SA: Association between PTGS2 polymorphism and autism spectrum disorders in Korean trios. Neurosci Res 2009, 62:66-69.

[98] Gu B, Desjardins P, Butterworth RF: Selective increase of neuronal cyclooxygenase-2 (COX-2) expression in vulvenerable brain regions of rats with experimental Wernicke's encephalopathy: effect of numesulide. Metab Brain Dis 2008, 23:175-187.

[99] Yaday UC, Subramanyam S, Ramana KV: Prevention of endotoxin-induced uveitis in rats by benfotiamine, a lipophilic analogue of vitamin B1. Invest Ophthalmol Vis Sci 2009, 50:2276-2282.

[100] Yaday UC, Kalariya NM, Srivastava SK, Ramana KV: Protective role of benfotiamine, a fat-soluble vitamin B_1

analogue, in lipopolysaccharide-induced cytotoxic signals in murine macrophages. Free Radic Biol Med 2010, 48:1423-1434.

[101] Chauhan A, Chauhan V, Brown WT, Cohen I: Oxidative stress in autism: increased lipid peroxidation and reduced serum levels of ceruloplasmin and transferrin--the antioxidant proteins. Life Sci 2004, 75:2539-2549.

[102] González-Fraguela M, Hung M, Vera H, Maragoto C, Noris E. Blanco L Galvizu R, Robinson, M: Oxidative stress markers in children with autism spectrum disorders. British J Med Medical Res 2013, 3:307-317.

[103] Sajdel-Sulkowska E, Lipinski B, Windom H, Audhya J, McGinnis W: Oxidative stress in autism: cerebellar 3 nitrotyrosine levels. Am J Biochem Biotechnol 2008, 4:73-84.

[104] Rose S, Melnyk S, Pavliv O, Bai S, Nick TG, Frye RE, James SJ: Evidence of oxidative damage and inflammation associated with low glutathione redox status in the autism brain. Transl Psychiatry 2012, 2:e134

[105] Ming X, Stein TP, Brimacombe M, Johnson WG, Lambert GH, Wagner GC: Increased excretion of a lipid peroxidation biomarker in autism. Prostaglandins Leukot Essent Fatty Acids 2005, 73:379-384.

[106] Yao Y, Walsh WJ, McGinnis WR, Praticò D: Altered vascular phenotype in autism: correlation with oxidative stress. Arch Neurol 2006, 63:1161-1164.

[107] Giulivi C, Zhang YF, Omanska-Klusek A, Ross-Inta C, Wong S, Hertz-Picciotto I, Tassone F, Pessah IN:Mitochondrial dysfunction in autism. JAMA 2010, 304:2389-2396.

[108] Yorbik O, Sayal A, Akay C, Akbiyik DI, Sohmen T: Investigation of antioxidant enzymes in children with autistic disorder. Prostaglandins Leukot Essent Fatty Acids 2002, 67:341-343.

[109] Al-Gadani Y, El-Ansary A, Attas O, Al-Ayadhi L: Metabolic biomarkers related to oxidative stress and antioxidant status in Saudi autistic children. Clin Biochem 2009, 42:1032-1040.

[110] James SJ, Melnyk S, Jernigan S, Cleves MA, Halsted CH, Wong DH, Cutler P, Bock K, Boris M, Bradstreet JJ, Baker SM, Gaylor DW: Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism. Am J Med Genet B Neuropsychiatr Genet 2006, 141B:947-956.

[111] Essa MM, Guillemin GJ, Waly MI, Al-Sharbati MM, Al-Farsi YM, Hakkim FL, Ali A, Al-Shafaee MS: Increased Markers of Oxidative Stress in Autistic Children of the Sultanate of Oman. Biol Trace Elem Res 2012, 147:25-27.

[112] Ming X, Johnson WG, Stenroos ES, Mars A, Lambert GH, Buyske S: Genetic variant of glutathione peroxidase 1 in autism. Brain Dev 2010, 32:105-109.

[113] Bowers K, Li Q, Bressler J, Avramopoulos D, Newschaffer C, Fallin MD: Glutathione pathway gene variation and risk of autism spectrum disorders. J Neurodev Disord 2011, 3:132-143.

[114] Williams TA, Mars AE, Buyske SG, Stenroos ES, Wang R, Factura-Santiago MF, Lambert GH, Johnson WG: Risk of autistic disorder in affected offspring of mothers with a glutathione S-transferase P1 haplotype. Arch Pediatr Adolesc Med 2007, 161:356-361.

[115] Frustaci A, Neri M, Cesario A, Adams JB, Domenici E, Dalla Bernardina B, Bonassi S: Oxidative stress-related biomarkers in autism: systematic review and meta-analyses. Free Radic Biol Med 2012, 52:2128-2141.

[116] Calingasan NY, Chun WJ, Park LC, Gibson GE: Oxidative stress is associated with region-specific neuronal death during thiamine deficiency. J Neuropathol Exp Neurol 1999, 58:946-958.

[117] Lukienko PI, Mel'nichenko NG, Zverinskii IV, Zabrodskaya SV: Antioxidant properties of thiamine. Bull Exp Biol Med 2000, 130:874-876.

[118] Portari GV, Marchini JS, Vannucchi H, Jordao AA: Antioxidant effect of thiamine on acutely alcoholized rats and lack of efficacy using thiamine or glucose to reduce blood alcohol content. Basic Clin Pharmacol Toxicol 2008, 103:482-486.

[119] Park DJ, West AR: Regulation of striatal nitric oxide synthesis by local dopamine and glutamate interactions. J Neurochem 2009, 111:1457-1465.

[120] West AR, Galloway MP, Grace AA: Regulation of striatal dopamine neurotransmission by nitric oxide: effector pathways and signaling mechanisms. Synapse 2002, 44:227-245.

[121] Söğüt S, Zoroğlu SS, Ozyurt H, Yilmaz HR, Ozuğurlu F, Sivasli E, Yetkin O, Yanik M, Tutkun H, Savaş HA, Tarakçioğlu M, Akyol O: Changes in nitric oxide levels and antioxidant enzyme activities may have a role in the pathophysiological mechanisms involved in autism. Clin Chim Acta 2003, 331:111-117.

[122] Lakshmi Priya MD, Geetha A: A biochemical study on the level of proteins and their percentage of nitration in the hair and nail of autistic children. Clin Chim Acta 2011, 412:1036-1042.

[123] Kim HW, Cho SC, Kim JW, Cho IH, Kim SA, Park M, Cho EJ, Yoo HJ: Family-based association study between NOS-I and -IIA polymorphisms and autism spectrum disorders in Korean trios. Am J Med Genet B Neuropsychiatr Genet 2009, 150B:300-306.

[124] Fillano JJ, Goldenthal MJ, Rhodes CH, Marin-Garcia J: Mitochondrial dysfunction in patients with hypotonia, epilepsy, autism, and developmental delay: HEADD syndrome. J Child Neurol 2002, 17:435-439.

[125] Oliveira G, Diogo L, Grazina M, Garcia P, Ataíde A, Marques C, Miguel T, Borges L, Vicente AM, Oliveira CR: Mitochondrial dysfunction in autism spectrum disorders: a population-based study. Dev Med Child Neurol 2005, 47:185-189.

[126] Jacobia SJ, Korotchkina LG, Patel MS: Characterization of a missense mutation at histidine-44 in a pyruvate dehydrogenase-deficient patient. Biochim Biophys Acta 2002, 1586:32-42.

[127] Naito E, Ito M, Takeda E, Yokota I, Yoshijima S, Kuroda Y: Molecular analysis of abnormal pyruvate dehydrogenase in a patient with thiamine-responsive congenital lactic academia. Pediatr Res 1994, 36:340-346.

[128] Naito E, Ito M, Yokota I, Saijo T, Matsuda J, Ogawa Y, Kitamura S, Takada E, Horii Y, Kuroda Y: Thiamine-responsive pyruvate dehydrogenase deficiency in two patients caused by a point mutation (F205L and L216F) within the thiamine pyrophosphate pyrophosphate binding region. Biochim Biophys Acta 2002, 1588:79-84.

[129] Bonne G, Benelli C, De Meirleir L, Lissens W, Chaussain M, Diry M, Clot JP, Ponsot G, Geoffroy V, Leroux JP, Marsac C: E1 pyruvate dehydrogenase deficiency in a child with motor neuropathy. Pediatr Res 1993, 33:284-288.

[130] Meléndez RR: Importance of water-soluble vitamins as regulatory factors of genetic expression. Rev Invest Clin 2002, 54:77-83. [Article in Spanish]

[131] Martin P, Singleton CK, Hiller-Stumhöfel S: The role of thiamine deficiency in alcoholic brain disease. Alcohol Res Health 2003, 27:174-181.

[132] Ishii K, Sarai K, Sanemori H, Kawasaki T: Concentration of thiamine and its phosphate esters in rat tissues determined by high pressure liquid chromography. J Nutr Sci Vitaminol (Tokyo) 1979, 25:517-523.

[133] Bubber P, Ke ZJ, Gibson GE: Tricarboxylic acid cycle enzymes following thiamine deficiency. Neurochem Int 2004, 45:1021-1028.

[134] Adams JB, Audhya T, McDonough-Means S, Rubin RA, Quig D, Geis E, Gehn E, Loresto M, Mitchell J, Atwood S, Barnhouse S, Lee W: Nutritional and metabolic status of children with autism vs. neurotypical children, and the association with autism severity. Nutr Metab (Lond) 2011, 8:34.

[135] Adams JB, Audhya T, McDonough-Means S, Rubin RA, Quig D, Geis E, Gehn E, Loresto M, Mitchell J, Atwood S, Barnhouse S, Lee W: Effect of a vitamin/mineral supplement on children and adults with autism. BMC Pediatr 2011, 11:111.

[136] Marui T, Funatogawa I, Koishi S, Yamamoto K, Matsumoto H, Hashimoto O, Jinde S, Nishida H, Sugiyama T, Kasai K, Watanabe K, Kano Y, Kato N: The NADH-ubiquinone oxidoreductase 1 alpha subcomplex 5 (NDUFA5) gene variants are associated with autism. Acta Psychiatr Scand 2011, 123:118-124.

[137] Shangari N, Mehta R, O'brien PJ: Hepatocyte susceptibility to glyoxal is dependent on cell thiamin content. Chem Biol Interact 2007, 165:146-154.

[138] Galdhar NR, Pawar SS: Hepatic drug metabolism and lipid peroxidation in thiamine deficient rats. Int J Vitam Nutr Res 1976, 46:14-23.

[139] Fraser DA, Hessvik NP, Nikolić N, Aas V, Hanssen KF, Bøhn SK, Thoresen GH, Rustan AC: Benfotiamine increases glucose oxidation and downregulates NADPH oxidase 4 expression in cultured human myotubes exposed to both normal and high glucose concentrations. Genes Nutr 2012, 7:459-469.

[140] Grosse W 3rd, Wade AE: The effect of thiamine consumption on liver microsomal drug-metabolizing pathways. J Pharmacol Exp Ther 1971, 176:758-765.

[141] Singh VK, Warren RP, Odell JD, Warren WL, Cole P: Antibodies to myelin basic protein in children with autistic behavior. Brain Behav Immun 1993, 7:97-103.

[142] Singh VK, Warren R, Averett R, Ghaziuddin M: Circulating autoantibodies to neuronal and glial filament proteins in autism. Pediatr Neurol 1997, 17:88-90.

[143] Stephenson DT, O'Neill SM, Narayan S, Tiwari A, Arnold E, Samaroo HD, Du F, Ring RH, Campbell B, Pletcher M, Vaidya VA, Morton D: Histopathologic characterization of the BTBR mouse model of autistic-like behavior reveals selective changes in neurodevelopmental proteins and adult hippocampal neurogenesis. Mol Autism 2011, 2:7.

[144] Gozzi M, Nielson DM, Lenroot RK, Ostuni JL, Luckenbaugh DA, Thurm AE, Giedd JN, Swedo SE: A magnetization transfer imaging study of corpus callosum myelination in young children with autism. Biol Psychiatry 2012, 72:215-220.

[145] Mostafa GA, Al-Ayadhi LY: A lack of association between hyperserotonemia and the increased frequency of serum anti-myelin basic protein auto-antibodies in autistic children. J Neuroinflammation 2011, 8:71.

[146] Markham JA, Herting MM, Luszpak AE, Juraska JM, Greenough WT: Myelination of the corpus callosum in male and female rats following complex environment housing during adulthood. Brain Res 2009, 1288:9-17.

[147] Mostafa GA, El-Sayed ZA, El-Aziz MM, El-Sayed MF: Serum anti-myelin-associated glycoprotein antibodies in Egyptian autistic children. J Child Neurol 2008, 23:1413-1438.

[148] Singer HS, Morris CM, Gause CD, Gillin PK, Crawford S, Zimmerman AW: Antibodies against fetal brain in sera of mothers with autistic children. J Neuroimmunol 2008, 194:165-172.

[149] Martin I, Gauthier J, D'Amelio M, Védrine S, Vourc'h P, Rouleau GA, Persico AM, Andres CR: Transmission disequilibrium study of an oligodendrocyte and myelin glycoprotein gene allele in 431 families with an autistic proband. Neurosci Res 2007, 59:426-430.

[150] Castellano B, Gonzalez B, Palacios G: Cytochemical demonstration of TPPase in myelinated fibers in the central and peripheral nervous system of the rat. Brain Res 1989, 492:203-210.

[151] Ishibashi S, Yokota T, Shiojiri T, Matunaga T, Tanaka H, Nishina K, Hirota H, Inaba A, Yamada M, Kanda T, Mizusawa H: Reversible acute axonal polyneuropathy associated with Wernicke-Korsakoff syndrome: impaired physiological nerve conduction due to thiamine deficiency? J Neurol Neurosurg Psychiatry 2003, 74:674-676.

[152] Gui QP, Zhao WQ, Wang LN: Wernicke's encephalopathy in nonalcoholic patients: clinical and pathologic features of three cases and literature reviewed. Neuropathology 2006, 26:231-235.

[153] Jiang H, Guo W, Liang X, Rao Y: Both the establishment and the maintenance of neuronal polarity require active mechanisms: critical roles of GSK-3beta and its upstream regulators. Cell 2005, 120:123-135.

[154] Yuskaitis CJ, Beurel E, Jope RS: 1. Evidence of reactive astrocytes but not peripheral immune system activation in a mouse model of Fragile X syndrome. Biochim Biophys Acta. 2010, 1802:1006-1012.

[155] Min WW, Yuskaitis CJ, Yan Q, Sikorski C, Chen S, Jope RS,

Bauchwitz RP: Elevated glycogen synthase kinase-3 activity in Fragile X mice: key metabolic regulator with evidence for treatment potential. Neuropharmacology 2009, 56:463-472.

[156] Mines MA, Yuskaitis CJ, King MK, Beurel E, Jope RS: GSK3 influences social preference and anxiety-related behaviors during social interaction in a mouse model of fragile X syndrome and autism. PLoS One 2010, 5:e9706.

[157] Beaulieu JM, Zhang X, Rodriguiz RM, Sotnikova TD, Cools MJ, Wetsel WC, Gainetdinov RR, Caron MG: Role of GSK3 beta in behavioral abnormalities induced by serotonin deficiency. Proc Natl Acad Sci U S A 2008, 105:1333-1338.

[158] Ciani L, Salinas PC: WNTs in the vertebrate nervous system: from patterning to neuronal connectivity. Nat Rev Neurosci 2005, 6:351-362.

[159] Zhang Y, Sun Y, Wang F, Wang Z, Peng Y, Li R:Downregulating the Canonical Wnt/β-catenin Signaling Pathway Attenuates the Susceptibility to Autism-like Phenotypes by Decreasing Oxidative Stress. Neurochem Res 2012, 37:1409-1419

[160] Zhao J, Sun X, Yu Z, Pan X, Gu F, Chen J, Dong W, Zhao L, Zhong C: Exposure to pyrimidine increases beta-amyloid accumulation, Tau hyperphosphorylation, and glycogen synthetase kinase-3 activity in the brain. Neurotox Res 2010, 19:575-583.

[161] 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 2010, 133:1342-1351.

[162] Walker-Smith J, Andrews J. Alpha-1-antitrypsin, autism, and coeliac disease: Lancet 1972, 2:883-884.

[163] Russo AJ, Neville L, Wroge C: Low Serum Alpha-1 Antitrypsin (AAT) in Family Members of Individuals with Autism Correlates with PiMZ Genotype. Biomark Insights 2009, 4:45-56.

[164] Ali BH: Some pharmacological and toxicological properties of furazolidone.Vet Res Commun 1983, 6:1-11.

[165] Ali BH, Bartlet AL: Anorexia and antagonism of thiamin utilization in poultry treated with furazolidone. Q J Exp Physiol 1982, 67:437-448.

[166] Staley NA, Noren GR, Bandt CM, Sharp HL: Furazolidone-induced cardiomyopathy in turkeys. Association with a relative alpha1-antitrypsin deficiency. Furazolidone-induced cardiomyopathy in turkeys. Association with a relative alpha1-antitrypsin deficiency. Am J Pathol 1978, 91:531-544.

[167] Ali BH, Hassan T, Wasfi IA, Mustafa AI: Toxicity of furazolidone to Nubian goats. Vet Hum Toxicol 1984, 26:197-200.

[168] Czarnecki C: Cardiomyopathy in turkeys. Comp Biochem Physiol A Comp Physiol. 1984, 77:591-598.

[169] Martin J, Hadchouel M, Gaultier M, Luzeau R, Hugon R, Daguet J: An animal model for the study of human alpha-1-antitrypsin deficiency. Biomedicine 1976, 25:319-320.

[170] Schmechel DE: Art, alpha-1-antitrypsin polymorphisms and intense creative energy: blessing or curse? Neurotoxicology 2007, 28:899-914.

[171] Junaid MA, Kowal D, Barua M, Pullarkat PS, Sklower Brooks S, Pullarkat RK: Proteomic studies identified a single nucleotide polymorphism in glyoxalase I as autism susceptibility factor. Am J Med Genet A 2004, 131:11-17.

[172] Barua M, Jenkins EC, Chen W, Kuizon S, Pullarkat RK, Junaid MA: Glyoxalase I polymorphism rs2736654 causing the Ala111Glu substitution modulates enzyme activity--implications for autism. Autism Res 2011, 4:262-270.

[173] Boso M, Emanuele E, Minoretti P, Arra M, Politi P, Ucelli di Nemi S, Barale F: Alterations of circulating endogenous secretory RAGE and S100A9 levels indicating dysfunction of the AGE-RAGE axis in autism. Neurosci Lett 2006, 410:169-173.

[174] Bierhaus A, Humpert PM, Morcos M, Wendt T, Chavakis T, Arnold B, Stern DM, Nawroth PP: Understanding RAGE, the receptor for advanced glycation end products. J Mol Med (Berl) 2005, 83:876-886.

[175] Karachalias N, Babaei-Jadidi R, Rabbani N, Thornalley PJ: Increased protein damage in renal glomeruli, retina, nerve, plasma and urine and its prevention by thiamine and benfotiamine therapy in a rat model of diabetes. Diabetologia 2010, 53:1506-1516.

[176] Karachalias N, Babaei-Jadidi R, Kupich C, Ahmed N, Thornalley PJ: High-dose thiamine therapy counters dyslipidemia and advanced glycation of plasma protein in streptozotocin-induced diabetic rats. Ann N Y Acad Sci 2005, 1043:777-783.

[177] Stirban A, Negrean M, Stratmann B, Gawlowski T, Horstmann T, Götting C, Kleesiek K, Mueller-Roesel M, Koschinsky T, Uribarri J, Vlassara H, Tschoepe D: Benfotiamine prevents macro- and microvascular endothelial dysfunction and oxidative stress following a meal rich in advancedglycation end products in individuals with type 2 diabetes. Diabetes Care 2006, 29:2064-2071.

[178] Kihm LP, Müller-Krebs S, Klein J, Ehrlich G, Mertes L, Gross ML, Adaikalakoteswari A, Thornalley PJ, Hammes HP, Nawroth PP, Zeier M, Schwenger V:Benfotiamine protects against peritoneal and kidney damage in peritoneal dialysis. J Am Soc Nephrol 2011, 22:914-926.

[179] Polizzi FC, Andican G, Cetin E, Civelek S, Yumuk V, Burçak G: Increased DNA-Glycation in Type 2 Diabetic Patients: The Effect of Thiamine and Pyridoxine Therapy. Exp Clin Endocrinol Diabetes 2012, 120:329-934.