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The role of thiamine in schizophrenia

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Abstract: Objective: Review the relationship between thiamine and schizophrenia. Methods: Information was obtained from MEDLINE. Results: Nutritional status has been related to the development of schizophrenia. Genetic studies have identified numerous factors that link thiamine to schizophrenia, including the renin angiotensin system, heme oxygenase-1, advanced glycation end products, alpha-antitrypsin, coenzyme Q10, glycogen synthetase kinase-3, and the transcription factor p53. Thiamine has also been implicated in schizophrenia via its effects on matrix metalloproteinases, the Wnt/β-catenin signaling pathway, the mitogen-activated protein kinase pathways, the reduced form of nicotinamide adenine dinucleotide phosphate, prostaglandins, cyclooxygenase-2, reactive oxidative stress, and nitric oxide synthase. Conclusions: These data suggest a role of thiamine in patients with schizophrenia. Therefore, additional investigation of thiamine in schizophrenic patients is required.

Keywords: Thiamine, Schizophrenia, Transketolase, Vitamin B1

1. Introduction

Schizophrenia is devastating mental illness that is characterized by symptoms of disruptions in reality, such as hallucinations and delusions. Nutritional status has been related to the development of schizophrenia. Poor performance IQ mediates the relationship between poor nutrition at age 3 and interpersonal and schizotypal personality at age 23 [1]. Early environmental events may be relevant in the etiology of schizophrenia. An association between prenatal starvation and schizophrenia has been observed in Dutch and Chinese famines [2-4].The developing brain is vulnerable to reduced thiamine intake and that the period of vulnerability may be different for activity and avoidance learning [5]. These authors observed that rat pups that suckle from thiamine-deficient (TD) dams exhibited memory deficits. Thiamine deficiency degrades the link between spatial behavior and hippocampal synapsin I and phosphorylated synapsin I protein levels. These proteins regulateneuro-transmitter release, which has implicated in hippocampal-dependent learning [6]. The mammillary bodies (MBs) are important relay nuclei with limbic and extra-limbic connections. MBs play important roles in memory formation, and these nuclei are affected during thiamine deficiency [7]. MB abnormalities are observed in patients with schizophrenia [8-9]. The number of parvalbumin-immuno-reactive MB neurons is reduced by more than 50% in the postmortem brains of schizophrenics compared to matched control brains [9]. Acute sulbutiamine injection increased thiamine triphosphate (TTP) in rat tissues [10] and induced a modulatory effect on glutamatergic and dopaminergic cortical transmissions in the rat brain [11]. Severe thiamine deficiencies, such as Wernicke encephalopathy and Beriberi heart disease, are observed in patients with schizophrenia [12-15]. Gontzeaet al. [16] assessed the thiamine status of patients with neurosis in a psychiatric department and observed a decreased in thiamine excretion and erythrocyte transketolase activity in neurotic patients compared to healthy control participants. These observations suggest the presence of thiamine deficiencies in these psychiatric patients. Erythrocyte transketolase abnormalities are also observed in schizophrenic patients [17-18]. Benton et al. [19] observed a significant association between improved thiamine status and enhanced performance across a range of cognitive-function tests in women in a controlled trial. These authors observed significant cognitive deteriorations in the psychoneurotic scales of the Minnesota Multiphasic Personality Inventory (MMPI) in thiamine deprived participants. However, thiamine supplementation reverses these effects [20], and thiamine supplementation improves the symptoms of neurotic patients [21]. Mice treated with thiamine tetrahydrofurfuryl disulfide (TTFD) exhibit decreased locomotor activity in solitary open-field testing.

TTFD-treated mice engage in more passive cuddling-type behaviors than vigorous play-type behaviors and exhibit a diminished startle response to loud noises [22]. Sacks et al. [23] demonstrated that a combination of acetazolamine and thiamine improved clinical presentation by reducing or eliminating hallucinations, delusions, and bizarre behaviors in most schizophrenic patients. Acetazolamide alone produced little benefit in one schizophrenic patient, but acetazolamine treatment in combination with thiamine in the same patient produced significant clinical improvement. A TD female patient developed auditory hallucinations, persecution delusion, catatonic stupor, and catalepsy. Her psychosis was ameliorated by repetitive intravenous thiamine administrations [24]. These results suggest a relationship between thiamine and schizophrenia. Therefore, we review the role of thiamine in schizophrenia in the present paper.

2. The Genomic Factors Associated with Thiamine in the Development of Schizophrenia

Genetic studies provide an excellent opportunity to associate molecular variations with epidemiological data. DNA sequence variations such as polymorphisms exert modest and subtle biological effects.

The primary function of the renin angiotensin system (RAS) is to maintain fluid homeostasis and regulate blood pressure. Several components of the RAS and its receptors are expressed in the central nervous system (CNS) [25-28], suggesting the important of RAS in the brain. Prepulse inhibition (PPI) is a measure of sensori-motor gating, which is disrupted in patients with schizophrenia (PPI) [29]. Angiotensin-converting enzyme (ACE) interacts with dopaminergic mechanisms in the brain to modulate PPI in mice [30]. Cerebrospinal fluid (CSF) ACE is significantly correlated with the length of schizophrenic psychosis [31]. Elevated CSF ACE and plasma renin activity are observed during antipsychotic drug treatment in schizophrenic patients [32-33]. Genotype distribution is significantly different in males with schizophrenia compared to male controls. The frequencies of the *DD* genotype and *D* allele are higher than those of the *II* genotype and *I* allele in schizophrenic males [34]. A modest association between *ACE* polymorphism and polydipsia has been demonstrated for schizophrenic patients [35]. An interaction between thiamine and the RAS has been observed. Thiamine deficiency significantly depresses plasma and urinary aldosterone responses to sodium deprivation in rats [36]. Thiamine attenuates hypertension and metabolic abnormalities in spontaneous hypertensive rats (SHRs). Thiamine repletion down-regulates the expression of angiotensinogen (-80%), ACE (-77%), and angiotensin type 1 receptor (-72%) mRNA transcripts in SHRs [37]. These observations suggest an effect of thiamine on ACE activity in schizophrenia.

Heme oxygenase-1 (HO-1) is a stress protein that may confer cytoprotection by enhancing the catabolism of pro-oxidant hemeby the radical-scavenging bile pigments biliverdin and bilirubin. The HO-1 gene is up-regulated by a host of noxious stimuli and is induced in CNS tissues that are affected by neurological diseases [38]. Basal HO-1 expression is low in the normal brain and is restricted to small groups of scattered neurons and neuroglia [39]. Schizophrenic-like features are observed in transgenic mice that overexpress human HO-1 in the astrocytic compartment [40]. Similarly, thiamine deficiency produces region-specific neuronal loss and HO-1 induction in microglia [41-42]. Thiamine administration inhibits further neuronal loss and the induction of HO-1-positive microglia, but other microglial changes persist [43].

The p53 gene and protein play critical roles in the regulation of the normal cell cycle, cell cycle arrest, and apoptosis. The p53 protein is to serve as a critical regulator of neuronal apoptosis in the CNS [44]. The p53 gene is a candidate susceptibility gene in schizophrenia [45]. Significant associations between the p53 gene and schizophrenia are observed in case-control and family-based samples [46]. Polymorphisms in p53 are observed schizophrenic patients [47-49]. P53 variants contribute to abnormal metabolic activity and white matter in the frontal lobe of schizophrenic patients [50]. By contrast, an increased number of thiamine transporters are observed in cells that over-express thiamine transport genes (mTHTR-1) and in cells that are exposed to conditions that induce DNA damage or p53 activation [51]. Thiamine diphosphate (TDP) inhibits p53 binding, and thiamine inhibits intracellular p53 activity [52]. Thiamine treatment significantly decreases p53 expression in cultured retinal neurons from diabetic rats [53]. These observations suggest that the transcription factor p53 is activated in schizophrenia with an increasing apoptotic response from cellular damage and that thiamine ameliorates these effects on cells.

Alpha-1 antitrypsin (ATT) is the most abundant circulating serine protease inhibitor. The ATT activity is enhanced in patients with schizophrenia [54-57]. A significant difference in phenotype and gene frequencies is observed between schizophrenic patients with and without a family history of schizophrenia. A significant increase in the M1 gene and a decrease in M2 gene are observed in patients with a family history of schizophrenia [58]. The ATT polymorphism with a non-MM genotype significantly increased the incidence of thiamine deficiency [59].

Coenzyme Q10 (CoQ10 or ubiquinone) is an electron carrier of the mitochondrial respiratory chain with antioxidant properties. The erythrocyte levels of CoQ10 were low in patients with schizophrenia [60]. In the TD liver, the concentration of ubiquinone is nearly doubled and a thiamine supplement promptly decreases levels to that of controls [61].

Glycogen synthetase kinase-3(GSK3) is a protein kinase that is involved in many physiological processes (e.g., metabolism, gene expression and apoptosis). Dysfunction

of protein kinase FA/GSK-3α was reported in lymphocytes of patients with schizophrenic disorder [62]. Hippocampal GSK-3α and GSK-3β mRNA levels were significantly lower (22% and 28%, respectively) in the tissue from the schizophrenic patients compared with the normal controls [63]. A significant reduction in CSF GSK-3β protein levels was reported in schizophrenic patients compared to healthy subjects [64]. GSK-3β protein levels were also reduced in the frontal cortex of rats with the neonatal excitotoxic hippocampal lesion used as a model of schizophrenia and in schizophrenic patients [65-67]. Exposure to pyrithiamine, an anti-thiamine compound, also increases the β-amyloid protein accumulation and GSK3 activity in the brain [68]. Benfotiamine improved cognitive function, reduced amyloid deposition, and suppressed GSK3 activity in an animal model of Alzheimer's disease [69]. These findings suggest that thiamine may influence schizophrenia by suppressing GSK3 activity.

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. 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 [70]. Arai et al. [71] isolated DNA from peripheral blood and post-mortem brain tissue of schizophrenic patients, they detected genetic and function alterations in Glyo-1 that associated with marked reductions in enzyme activity. Genetic abnormalities in Glyo-1 are associated with patients with schizophrenia [72-74]. Soluble RAGEs were elevated in patients with schizophrenia [75]. RAGE gene polymorphism is associated with schizophrenia [76]. Thiamine and a benfotiamine supplement prevented tissue accumulation and increased the urinary excretion of protein glycation, oxidation and nitration adducts associated with experimental diabetes [77]. Karachalias et al. [78] 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 (STZ) 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 [79]. The addition of benfotiamine enhanced transketolase activity and decreased the expression of AGE and RAGE in a peritoneal dialysis model of uremic rats [80]. 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 [81].

3. The Non-Genomic Role of Thiamine in Schizophrenia

Matrix metalloproteinases (MMPs) are proteolytic enzymes that are responsible for extracellular matrix remodeling and the regulation of leukocyte migration through the extracellular matrix, which is an important factor involved in inflammatory processes and infectious diseases. MMPs are produced by many cell types including lymphocytes, granulocytes, astrocytes and activated macrophages. A high frequency of positive-MMP-9 activity was detected in serum in patients with schizophrenia [82]. Autoantibodies from schizophrenia patients induce MMP-3 production in the rat frontal cortex [83]. A significant functional MMP-9 polymorphism has been observed in schizophrenic patients compared to healthy controls [84]. MMP-9 is also up-regulated in the TD mouse brain [41-42]. Studies were performed in vulnerable (medial thalamus) versus spared (frontal cortex) regions of the brain. The hemorrhagic lesions and a concomitant loss in protein expression of occluding, such as zonaoccludens, were observed in the medial thalamus of TD- mice. MMP-9 levels were also selective increased in the medial thalamus of these animals, and were found to be localized in the vascular endothelium, as well as in PMNCs [85]. Thiamine prevents diabetes-induced cardiac fibrosis and decreases MMP-2 activity in the hearts of diabetic rats [86]. Thiamine and benfotiamine correct the increases in MMP-2 activity that result from high glucose levels in human retinal pericytes and increase TIMP-1 [87]. Fursutiamine, a vitamin B1 derivative, enhances the chondroprotective effects of glucosamine hydrochloride and chondroitin sulfate and reduces the level of MMP-1 in rabbit experimental osteoarthritis [88].

The mitogen-activated protein kinase (MAPK) pathways provides a key link between the membrane-bound receptors that receive these cues and changes in the pattern of gene expression, including the extracellular signal-regulated kinase (ERK) cascade, the stress-activated protein kinases/c-jun N-terminal kinase (SAPK/JNK) cascade, and the p38 MAPK/RK/HOG cascade [89]. MAPK levels are elevated in the cerebellar vermis of postmortem schizophrenic subjects compared to normal subjects [90]. Benfotiamine modulates the macrophage response to bacterial endotoxin-induced inflammation by preventing the activation of p-38 MAPK and stress-activated kinases (SAPK/JNK) [91].

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, via the generation of reactive oxygen species (ROS) from molecular oxygen. NOX is widely expressed in various immune cells, such as microglia, macrophages, and neutrophils. The dorsolateral prefrontal cortex of schizophrenic patients exhibits a significant decrease in NADPH-expressing neurons in the superficial white matter

and the overlying cortex. However, a significant increase in NADPH-expressing neurons is observed in white matter below the cortex. [92].Distorted distribution of NADPH-neurons was also found in the lateral temporal lobe [93]. NADPH levels in mediodorsal thalamus of postmortem schizophrenic patients are reduced compared to controls [94]. The NADPH quinine oxidoreductase 1 (NQO1) gene polymorphism (609C/T) increases the susceptibility to the development of tardive dyskinesia in schizophrenia, but this polymorphism is not associated with the development of schizophrenia in the Korean population [95]. Behrens and Sejnowski [96] suggest that the persistent activation of the IL-6/Nox2 pathway is an environmental factor that tips the redox balance toward schizophrenic symptoms during late adolescence and early adulthood in individuals with genetic predisposition. Thiamine is an essential coenzyme for transketolase, which is part of the pentose phosphate pathway that maintains cellular NADPH levels. Thiamine is cytoprotective and restores NADPH levels, glyoxal detoxification and mitochondrial membrane potential in hepatocytes with glyoxal toxicity [97]. NADPH cytochrome c-reductase levels are increased in TD animals [98]. Benfotiamine treatment under normo- and hyper-glycemic conditions significantly down-regulates Nox4 expression [99]. Animals that are fed a high-thiamine diet exhibit approximately 57% of the NADPH-cytochrome c reductase activity of animals that are fed a TD diet [100]. The data suggest a role for thiamine in, protecting schizophreniavia the regulation of NADPH-cytochrome c activity.

Prostaglandins (PGs) participate in inflammatory processes. Cyclooxygenase(COX) convertsarachidonic acid into PGs. These released prostanoids play an important role in normal neural function, including spatial learning, synaptic plasticity and long-term potentiation [101]. Autoantibodies from schizophrenic patients induce PGE_2 production in the rat frontal cortex [83]. Schizophrenic patients exhibit higher plasma levels of pro-inflammatory PGE_2 than age-matched controls [102]. COX-1 and prostaglandin-endoperoxide receptor 3 (PTGER3) mRNA expression are increased in older schizophrenic patients (> 40 years of age) compared to matched controls and younger schizophrenic patients (< 40 years of age) [103]. A prospective double-blind study revealed that COX-2 inhibitor add-on therapy produces significantly greater improvements in Positive and Negative Syndrome Scale (PANSS) scores and all subscales during the acute phase compared torisperidone therapy alone in schizophrenic patients [104-105]. A significantly better outcome was observed in early stage schizophrenic patients who were treated with amisulpride plus celecoxib compared patients who received amisulpride plus placebo [106]. Moreover, the expressions of COX-2 mRNA and $PGE_2$are selectively increased in vulnerable regions during the symptomatic stages of TD encephalopathy in animal models [107]. Up-regulation of 15-hydroxyprostaglandin dehydrogenase (15-PGDH) expression was observed in breast cancer cell lines transfected with thiamine transporter (*THTR2*) gene and down-regulation was observed after suppression of *THTR2* with siRNA vectors [108]. Over-expressed of 15-PGDH inhibited IL-1β-induced COX-2 expression [109]. Benfotiamine inhibits the expression of COX-2 in endotoxin-induced uveitis in rats [110]. Benfotiamine also blocks the expression of COX-2 and its PGE_2product in murine macrophages in a LPS-induced cytotoxicity model [91].

Reactive oxygen species (ROS) play a major role in various cell-signaling pathways. ROS activates various transcription factors and increases the expression of proteins that control cellular transformation, tumor cell survival, tumor cell proliferation and invasion, angiogenesis, and metastasis. Altered antioxidant enzymes and oxidative stress are associated with schizophrenic patients. Increased levels of lipid peroxidation in plasma, red blood cells (RBCs), and cerebrospinal fluid are reported in schizophrenic patients [111-114]. Elevated plasma superoxide dismutase (SOD) activities are observed in first-episode and drug naïve schizophrenic patients compared to controls [115]. Serum SOD activity is also significantly increased in schizophrenic patients compared to controls [116]. An association between polymorphismsin the manganese-containing SOD (Mn-SOD) gene and schizophrenia has been observed [117], suggesting that an Mn-SOD variant contributes to the physiopathogenesis of schizophrenia. A significant increase in malondialdehyde (MDA) levels has been observed in schizophrenic patients, compared to age-matched control group [118]. Similarly, oxidative stress is associated with region-specific neuronal death, and lipid peroxidation products accumulate in the remaining thalamic neurons after 11 days in TD animal models [119].Cardiac oxidative stress is involved in TD-induced heart failure rats; Intracellular cardiac superoxide, SOD protein, and H_2O_2 contents are increased while GSH peroxidase activity is decreased [120]. Thiamine inhibits lipid peroxidation and the free radical oxidation of oleic acid in rat liver microsomes *in vitro* [121]. In one study, male Wistar rats were intoxicated with a dose of ethanol; the levels of MDA, reduced glutathione and vitamin E were measured as parameters of the antioxidant system of the liver and were improved in the thiamine-treated group [122].Thiamine supplement suppressesparaquat -induced Mn-SOD and glucose-6-phosphate dehydrogenase *in vitro* [123].

Nitric oxide synthase (NOS) synthesizes nitric oxide (NO), which regulates a variety of important physiological responses, including cell migration, the immune response, and apoptosis.NO affects the development and function of the CNS. NO enhances dopamine release in the striatum in animal models [124]. Extracellular dopamine release increases following the intra-striatal infusion of NOS substrates [125]. NOS concentrations are increased in the cerebellar vermis in postmortem brain tissue of schizophrenic patients compared to controls [126]. NOS variants are associated with schizophrenia [127-129]. Auto antibodies from schizophrenia patients induce NO production in the rat frontal cortex [83]. A remarkable

increase in RBC NO levels is observed in schizophrenic patients compared to control subjects [130]. Reduced plasma levels of glutathione (GSH) are significantly lower in schizophrenic patients compared to controls [131]. Glutathione deficiency during postnatal development reduces parvalbumin expression in a subclass of γ-amino butyric acid (GABA) neurons in the anterior cingulate cortex in an animal model of schizophrenia [132]. GSH S-transferase polymorphisms are a risk factor for schizophrenia [133]. Endothelial NOS gene deletion restores blood brain barrier integrity and attenuates neurodegeneration in the TD mouse brain [42]. Benfotiamine inhibits iNOS expression in endotoxin-induced uveitis in rats [107]. Benfotiamine also inhibits iNOS expression in an LPS-induced cytotoxicity model in murine macrophages [91]. Thiamine improves reduced GSH levels in acutely alcoholic rats [122].

4. Conclusions

In the present paper, the relationship between thiamine and schizophrenia is reviewed. Genetic studies provide opportunities to determine which proteins link thiamine to a schizophrenic pathology. The effects of thiamine are mediated by numerous non-genomic mechanisms, including effects on protein expression, oxidative stress, inflammation, and cellular metabolism. However, thiamine absorption decreases with advancing age [134]. Patients in the early stages of thiamine-deficient encephalopathy (Wernicke's encephalopathy) rapidly respond to large doses of parental thiamine. The initial doses of thiamine are generally 100 mg two to three times daily for 1 to 2 weeks. Therefore, further investigations of thiamine in schizophrenic patients are required, and a cautious approach is advisable before recommending the widespread use of thiamine in schizophrenic patients.

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