Journal of the Neurological Sciences 316 (2012) 1–8

Contents lists available at SciVerse ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review article

Thiamine and Parkinson's disease

Khanh vinh quốc Lương *, Lan Thi Hoàng Nguyễn

Vietnamese American Medical Research Foundation, Westminster, CA, USA

ARTICLE INFO

Article history:
Received 2 September 2011
Received in revised form 3 February 2012
Accepted 8 February 2012
Available online 2 March 2012

Keywords:
Thiamine
Parkinson's disease
Movement disorder
Transketolase

ABSTRACT

Parkinson's disease (PD) is the second most common form of neurodegeneration in the elderly population. PD is clinically characterized by tremors, rigidity, slowness of movement and postural imbalance. A significant association has been demonstrated between PD and low levels of thiamine in the serum, which suggests that elevated thiamine levels might provide protection against PD. Genetic studies have helped identify a number of factors that link thiamine to PD pathology, including the *DJ-1* gene, excitatory amino acid transporters (EAATs), the α-ketoglutarate dehydrogenase complex (KGDHC), coenzyme Q10 (CoQ10 or ubiquinone), lipoamide dehydrogenase (LAD), chromosome 7, transcription factor p53, the renin–angiotensin system (RAS), heme oxygenase-1 (HO-1), and poly(ADP-ribose) polymerase-1gene (*PARP-1*). Thiamine has also been implicated in PD through its effects on L-type voltage-sensitive calcium channels (L-VSCC), matrix metalloproteinases (MMPs), prostaglandins (PGs), cyclooxygenase-2 (COX-2), reactive oxygen species (ROS), and nitric oxide synthase (NOS).

Recent studies highlight a possible relationship between thiamine and PD. Genetic studies provide opportunities to determine which proteins may link thiamine to PD pathology. Thiamine can also act through a number of non-genomic mechanisms that include protein expression, oxidative stress, inflammation, and cellular metabolism. Further studies are needed to determine the benefits of using thiamine as a treatment for PD.

Contents

1. Introduction

Parkinson's disease (PD) is a movement disorder characterized by tremors, rigidity, slowness of movement and postural imbalance. The primary pathologic abnormalities are the loss of the pigmented cells of the substantia nigra (SN) pars compacta and the dopaminergic neurons of the striatum, which decreases in dopamine levels. The most effective treatment for PD is levodopa in combination with a peripheral decarboxylase inhibitor (carbidopa or benserazide). Dopamine has been reported to suppress the mouse-killing aggression (muricide) induced by a thiamine-deficient (TD) diet [1]. This suppressive effect can be potentiated with carbidopa [2]. Patients with PD that have undergone levodopa therapy show significantly higher cerebrospinal fluid (CSF) levels of thiamine diphosphate (TDP) and total thiamine than those patients who are not treated with this drug [3]. Moreover, thiamine deficiency can decrease the concentration of dopamine in the striatum, whereas animals fed on a diet that contained 5% ethanol show increased dopamine turnover [4]. In an experimental TD study, a region-specific vesicular dysfunction, i.e., decreased levels of dopaminergic metabolites, was seen [5]. Intrastriatal administration of thiamin triphosphate (TTP) or TDP induces dopamine release [6]. These findings suggest a relationship

* Corresponding author at: 14971 Brookhurst St. Westminster, CA 92683, USA. Tel.: +1 714 839 5898; fax: +1 714 839 5989.
E-mail address: Lng2687765@aol.com (K.V.Q. Lương).

0022-510X/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.jns.2012.02.008

between thiamine and dopamine. Therefore, we reviewed the role of thiamine in PD patients.

2. Genomic factors associated with thiamine in Parkinson's disease

DJ-1 has a number of reported functions, including cellular transformations, transcriptional effects, mRNA stability control, and oxidative stress responses. Mutations in *DJ-1* have been reported to be associated with PD [7,8]. DJ-1 orthologs in a variety of eukaryotic species are similar to the bacterial *thiJ* gene, which encodes a thiamine biosynthesis enzyme [9,10].

Glutamate is a major excitatory neurotransmitter in the CNS and is known to be neurotoxic when present in excess levels at the synapses. Synaptic glutamate is removed by cytoplasmic membrane protein known as excitatory amino acid transporters (EAATs). Nigral dopamine neurons have been reported to express EAATs [11]. A deficiency of EAATs has been associated with reduced glutathione (GSH) levels and increased oxidant levels, as well as neurodegeneration in the hippocampus at an advanced age [12]. EAAT dysfunction can trigger GSH depletion, which ensures astrocyte oxidative death and mesencephalic dopamine neuron vulnerability [13,14]. GSH depletion is suggested to be a primary event in the pathogenesis of PD [15]. In the ventral mesencephalon, the highest levels of EAAT expression are in the SN, particularly in the pars compacta, where the majority of grain clusters overlay the large pigmented dopaminergic neurons that degenerate in PD [16]. This morphology suggests that EAATs may be involved in the pathogenesis of PD. Moreover, gene encoding glutamate transporters have been shown to be downregulated in TD astrocytes [17].

The α-ketoglutarate dehydrogenase complex (KGDHC) is an important mitochondrial constituent and is the rate-regulating enzyme of the Krebs cycle. KGDHC deficiency is likely to impair brain energy metabolism and, therefore, brain function. In PD, many melanized neurons show reduced immunostaining for KGDHC in the SN, which roughly correlates with the severity of degeneration [18]. Mizuno et al. [19] also reported a loss of the KGDHC in the SN and implicated oxidative stress as an important contributor to nigral cell death in PD. Inhibiting KGDHC by either methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 5-S-cysteinyldopamine may contribute to mitochondrial dysfunction and cell death in PD [20,21]. Similarly, decreased KGDHC activities were observed in the brains of TD animal models and in postmortem human brain [22–24]. Impaired motor performance on a rotarod was apparent at 8 days of TD and was severe 10 days of TD, in which the overall KGDHC activity declined 52% in the submedial thalamic nucleus [17].

Coenzyme Q10 (CoQ10 or ubiquinone) is an electron carrier of the mitochondrial respiratory chain with antioxidant properties. Levels of CoQ10 are reported to be reduced in blood, platelets, and the cortex of patients with PD [25–28]. In the CSF, the percentage of oxidized to total CoQ10 of patients with PD was significantly higher than in the control group [28]. In addition, CoQ10 provided neuroprotection from iron, MPTP, paraquat, and dichlorvos in dopaminergic neurons [29–32]. These findings suggest that mitochondrial oxidative damage may play an important role in the pathogenesis of PD. In the TD liver, the concentration of ubiquinone is nearly doubled and a thiamine supplement promptly decreases levels to that of controls [33]. Moreover, lipoamide dehydrogenase (LAD) has been shown to be involved in the conversion of ubiquinone (CoQ10, oxidized form) into ubiquinol (reduced form) and has a role in MPTP-induced neurotoxicity [34]. LAD-deficient mice have increased vulnerability to MPTP, malonate, and nitropionic acid neurotoxicity [35]. Congenital LAD deficiency has been found in muscles and fibroblasts; some patients have moderate motor impairment and respond well to thiamine treatment [36–38]. Furthermore, chromosome 7 is the location of genes for sporadic PD, LAD, and human thiamine pyrophosphokinase cDNA [39–41] and also regulates dopaminergic amacrine cell numbers in the mouse retina [42].

Selective cell death of dopaminergic neurons in the SN is the major cause of PD. P53 is a transcription factor that has a major role in determining cell fates in response to DNA damage. The p53 protein level in the caudate nucleus has been shown to be significantly higher in patients with PD than in controls [43]. A 3-fold increase in p53 phosphorylation is seen in dopamine-induced apoptosis of cerebellar granule neurons [44]. Nakaso et al. [45] showed that p53 activity may correlate with neuronal death via the mitochondrial pathway in a model of PD. Inhibitors of the tumor suppressor protein p53 are highly effective in protecting midbrain dopaminergic neurons and improving behavioral outcome in a mouse model of PD [46]. Increased thiamine transporter activities have been found in cells that overexpress the genes that code for thiamine transporters (mTHTR-1) and under conditions of DNA damage or p53 activation [47]. TDP has been shown to inhibit p53 binding and thiamine has been shown to inhibit intracellular p53 activity [48]. The expression of p53 is decreased significantly in cultured retinal neurons of diabetic rats treated with thiamine [49].

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 found in the CNS [50–53], which suggests that it may be involved in brain activity. CSF levels of angiotensin-converting enzyme (ACE) activity decrease in PD patients and increase with dopaminergic treatments [54,55]. In addition, an ACE inhibitor, perindopril, has been shown to exert beneficial effects on the dopaminergic system [56,57]. After four weeks of treatment with perindopril, patients with PD had a faster onset of motor response to L-dopa and a reduction in “on phase” peak dyskinesia [58]. Furthermore, the frequency of the homozygous DD genotype of the ACE gene is significantly increased in patients with PD compared to controls, an effect that is also seen in PD patients with L-dopa-induced psychosis [59,60]. Other studies, however, have revealed no association between ACE polymorphisms, PD and L-dopa-induced adverse effects [61,62]. The difference in these reports may be related to racial and ethnic groups, i.e., Chinese vs. Caucasian populations. Thiamine attenuates the hypertension and downregulates the expression levels of the mRNA transcription of angiotensinogen and angiotensin type 1 receptors in a defective CD36 gene of the spontaneous hypertensive rat (SHR) [63].

Heme oxygenase-1 (HO-1) is a stress protein that may confer cytoprotection by enhancing the catabolism of pro-oxidant heme into the radical scavenging bile pigments biliverdin and bilirubin. The HO-1 gene is susceptible to upregulation by a host of noxious stimuli and is induced in CNS tissues affected by neurological diseases [64]. In the normal brain, basal HO-1 expression is low and restricted to small groups of scattered neurons and neuroglia [65]. In PD brain, HO-1 is highly overexpressed in astrocytes within the SN and Lewy bodies of affected dopaminergic neurons [66]. Serum HO-1 levels are reported to increase in PD patients but not in Alzheimer's disease patients [67], which suggests a systemic antioxidant reaction related to a chronic oxidative stress state in PD. Similarly, thiamine deficiency produces region specific neuronal loss and HO-1 induction in microglia [68,69]. Thiamine administration blocks further neuronal loss and the induction of HO-1 positive microglia, while other microglial changes persist [70].

Poly(ADP-ribose) polymerase-1 (PARP-1) is a nuclear protein that contributes to both neuronal death and survival under stressful conditions. Overexpression of PARP has been reported in dopaminergic neurons of the SN in PD patients [71]. PARP participates in MPTP-induced neurotoxicity in vivo [72]. MPTP is a neurotoxin that causes parkinsonism in humans and animals; mice lacking the PARP gene are dramatically spared from MPTP neurotoxicity [73]. Moreover, PARP inhibitors have been shown to be a valuable neuroprotective tool in models of PD [74,75]. PARP-1 variants are reported to be