Journal of
Alzheimer's Disease & Parkinsonism

Bunik VI, J Alzheimers Dis Parkinsonism 2014, 4:6
DOI: 10.4172/2161-0460.1000173

Mini Review Open Access

Benefits of Thiamin (Vitamin B1) Administration in Neurodegenerative Diseases May Be Due to Both the Coenzyme and Non-coenzyme Roles of Thiamin

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Received date: Nov 20, 2014, **Accepted date:** Dec 11, 2014, **Published date:** Dec 18, 2014

Abstract

Although no systematic studies on therapeutic value of thiamin administration in neurodegenerative diseases are available to draw statistically significant conclusion, beneficial effects of thiamin in the diseases have been observed in independent case reports. The data are usually interpreted as improvement of central metabolism due to the coenzyme role of thiamin diphosphate (ThDP) in the transketolase, pyruvate dehydrogenase and 2-oxoglutarate dehydrogenase reactions. However, several lines of evidence support a view that the thiamin action is not limited to this mechanism. First, no firm correlation between the benefits of thiamin administration and levels of ThDP and/or ThDP-dependent enzymes in brain has been shown. Second, synthesis of non-coenzyme derivatives of thiamin, such as thiamin triphosphate and its adenylated form, occurs in nature from bacteria to mammals. Third, emerging data suggest significance of the non-coenzyme derivatives of thiamin for cellular responses to metabolic stress and DNA damage. The review draws attention to importance of these new data for interpreting molecular mechanisms of the consequences of thiamine deficiency or supplementation.

Keywords: Thiamin in neurodegeneration; Thiamin-binding proteins; Adenylated thiamin triphosphate; Cholinergic neurotransmission; Glutamatergic neurotransmission

Thiamin administration improves cognitive function in neurodegenerative diseases

Transient improvement in cognitive function of some patients with neurodegenerative diseases, including Alzheimer disease (AD) and Parkinson disease (PD) has been observed upon administration of thiamin (vitamin B1) [1-4]. Often, very high doses were employed, such as ≥ 100-fold excess over the recommended daily dose. It is worth noting in this regard that levels of thiamin and its coenzyme form, thiamin diphosphate (ThDP) in humans are decreased with age [5], whereas in patients with AD and fronto-temporal dementia significantly less ThDP was determined in post-mortem cortex samples than in the age-matched controls [6,7]. Thus, aging is accompanied by decreased body thiamin, especially pronounced in neurodegenerative states, with thiamin administration potentially improving brain function in neurodegenerative patients. Although no systematic studies are available to draw a statistically significant conclusion on the benefits [8], a role of dietary thiamin in fighting AD-related alterations in brain attracts attention [9].

Molecular mechanisms of the thiamin action

The coenzyme action of thiamin

Thiamin in its diphosphorylated form is well-known as a coenzyme of the enzymes of central metabolism, such as cytosolic transketolase, and mitochondrial pyruvate and 2-oxoglutarate dehydrogenases. The three other systems which depend on the coenzyme action of thiamin in mammals, are the protein coded by the DHTKD1 gene recently characterized as 2-oxoadipate dehydrogenase [10-12], mitochondrial dehydrogenase of the branched chain 2-oxo acids and peroxisomal enzyme 2-hydroxyacyl-CoA lyase [13]. Although the latter enzymes are not considered as often as those involved in central energy metabolism, their mutations also lead to neurological disorders, supporting ThDP-dependent enzymes to be essential for normal brain function not only because of their role in energy production. Along with the mostly considered energy deficit due to malfunction of the cytoplasmic and mitochondrial enzymes of glucose oxidation in thiamin deficiency and its different models [14-16], these states are also characterized by impaired metabolism of major neurotransmitters, acetylcholine and glutamate [17]. Indeed, pyruvate dehydrogenase produces acetyl-CoA for acetylcholine synthesis, whereas 2-oxoglutarate dehydrogenase oxidizes the glutamate precursor 2-oxoglutarate. As a result, inhibition of pyruvate dehydrogenase decreased synaptosomal synthesis of acetylcholine [18], whereas inhibition of 2-oxoglutarate dehydrogenase changed glutamate and GABA levels in different systems including cultured primary neurons and rat brain [19,20]. More details on the ThDP-dependent enzymes in metabolic regulation and diseases are given in a recent review [17].

The non-coenzyme action of thiamine

Mammalian metabolism of thiamin includes the synthesis of the non-coenzyme derivatives of thiamin, thiamin degradation and redox transformations

Although to date the biological role of thiamin in mammals is limited to generation of the coenzyme ThDP, mammals do synthesize also other, i.e. non-coenzyme, derivatives of thiamin. These are the thiamin mono- and triphosphates (ThMP and ThTP) and adenylated thiamin tri- (AdThTP) or di- (AdThDP) phosphates [21]. However,

neither the synthesizing enzymes, nor molecular mechanisms or protein targets of their action are well-defined at molecular level. While ThMP is usually considered just as the hydrolysis product of ThDP, specific biological role of ThMP in mammals may be linked to the ThMP transport in blood plasma and penetration through the blood brain barrier [22]. Importance of this role of ThMP is supported by the energy-dependent synthesis of ThMP from thiamin in erythrocytes [23]. The data are accumulating that ThTP and its adenylated derivative may be involved in stress signaling and/or tissue-specific metabolic conditions. In particular, ThTP and AdThTP were shown to accumulate in bacterial system under stress conditions, such as carbon and amino acid starvation, supposedly acting as alarmones [24-26]. On the other hand, some animal tissues are known to possess high levels of ThTP under normal conditions [5,21]. Structural analysis of the only identified enzyme which metabolizes the non-coenzyme derivatives of thiamin, thiamin triphosphatase, indicated that it belongs to the enzyme family including the protein members which generate or hydrolyze the second messangers cAMP or tripolyphosphates [27]. Regulatory significance of these reactions is in line with similar functions of the non-coenzyme derivatives of thiamin.

Medical usage of the high doses of thiamin must also take into account that rapid degradation of thiamin resulting in 4-methyl-5-(2-hydroxyethyl)-thiazole or 4-methylthiazole-5-acetic acid, occurs after the thiamin injection in mammals [28]. The degradation products were determined in different mammalian tissues including brain, and also in germfree rats. The studies support the view that thiamin degradation, usually ascribed to intestinal microflora, is catalysed by mammalian enzymes as well. Mammalian systems also contain products of the thiamine oxidation, such as thiamin disulfide and thiochrome, which are easily oxidized in the presence of reactive oxygen and nitrogen species. In view of the antioxidant properties of thiamin in the presence of nitric oxide and peroxides, and high pharmacological efficiency of the synthetic thiamin open-ring forms with the hydrophobically modified thiol, such as benfotiamin or disulfides sulbuthiamin and fursulthiamin [21], regulatory significance of naturally occurring oxidized thiamin derivatives cannot be excluded [29].

Thus, improved brain function upon high-dose thiamin administration may rely not only on its role as a coenzyme in central metabolism, but also on the non-coenzyme binding of thiamin and its derivatives, including the products of degradation and redox modifications, to protein targets. Although some of these proteins have been recently identified, potential biological significance of the interactions has not received much attention. As a result, the protein targets binding thiamin and derivatives in a non-coenzyme mode remain largely unknown.

The thiamin-dependent regulation of phosphorylation of synaptic proteins involved in cholinergic neurotransmission

It has long been known that co-release of thiamin with acetylcholine occurs upon cholinergic neurotransmission, facilitating signal transduction [30-32]. This phenomenon should result in cyclic changes of the intracellular thiamin concentration upon the neurotransmission, which may be of regulatory significance by coupling neurotransmission to metabolism through both the coenzyme and non-coenzyme action of thiamin. Indeed, at physiologically relevant concentrations of 1-10 μM, thiamin addition to synaptosomes decreased synthesis of acetylcholine [18]. The decrease occurred concomitant with increased phosphorylation of pyruvate dehydrogenase, which leads to the enzyme inactivation causing decreased production of acetylcholine precursor acetyl-CoA. The inhibitory action of thiamin on the acetylcholine synthesis is in contrast to the expected coenzyme action of thiamin. That is, increased synthesis of the coenzyme ThDP from added thiamin should activate pyruvate dehydrogenase, increasing synthesis of acetylcholine due to activated production of its precursor acetyl-CoA. Thus, the experiment clearly indicates the regulation of acetylcholine synthesis through non-coenzyme action of synaptosomal thiamin on the pyruvate dehydrogenase phosphorylation. In independent experimental system, the non-coenzyme derivative of thiamin, ThTP, was shown to phosphorylate rapsyn [33], which is the acetylcholine receptor-scaffolding protein supporting synapse integrity [34]. Thus, the non-coenzyme action of thiamin in cholinergic neurotransmission is supported by the thiamin release into synaptic cleft and thiamin-dependent phosphorylation of metabolic and regulatory proteins involved. It may be suggested that changes in the intracellular thiamin concentration upon the thiamin co-release at cholinergic synapses may be associated with the changes of not only ThDP, but also ThTP and/or other non-coenzyme derivatives of thiamine, whose regulatory action facilitates neurotransmission.

Mammalian proteins beyond the known ThDP-dependent enzymes and thiamin transporters, which interact with thiamin and its derivatives

Several membrane proteins involved in neurotransmission, including the thiamin-binding protein with ThTPase activity [35], Na^+, K^+-ATPase and ion channels were supposed to interact with thiamin, its natural derivatives or structural analogs [36,21], although the data based on functional studies and/or binding to only partially purified proteins were inconsistent. Nevertheless, it is worth noting that Na^+, K^+-ATPase was inhibited by the thiamin analog widely used to create animal models of thiamin deficiency, pyrithiamin [37]. The thiamin interaction with the protein-bound radical species produced by hemoglobin and myoglobin [29] implies the thiamin binding site on these proteins. Cytosolic adenylate kinase was shown to catalyze synthesis of ThTP from ThDP in vitro [38], with the correlation between the levels of adenylate kinase 1 and ThTP observed in tissue possessing high ThTP level [39]. In other systems, however, adenylate kinase 1 did not seem to be involved in the physiologically relevant ThTP synthesis [40,25]. Nevertheless, in view of the in vitro data on the ThTP synthesis in the adenylate kinase reaction, discovery of multiple isoforms of adenylate kinase which differ in structure and localization [41], suggests some of the isoforms as potential candidates for the enzymes of the ThTP synthesis. Prion protein has recently been shown to bind thiamin [42,43]. In view of the pathophysiologically relevant interaction of prion with β-amyloid oligomers [44], the thiamin dependence of the process may be suggested to contribute to the non-coenzyme action of thiamin in AD. The thiamin involvement in pathogenicity of β-amyloid is further supported by an independent study indicating that another thiamin ligand, albumin [45], regulates β-amyloid peptide fiber growth in the brain interstitium [46]. Poly (ADP-ribose) polymerase-1 (PARP-1) was shown to be inhibited by micromolar concentrations of AdThTP. Because the enzyme is over activated under diabetes mellitus, the beneficial action of the high-dose thiamin treatment under this condition was suggested to be partly due to the PARP-1 inhibition by AdThTP [47]. Thus, the protein targets of the non-coenzyme action of thiamin and/or derivatives are emerging, with the field having a perspective to greatly advance due to the

modern high-throughput methods of protein identification, structural characterization and bioinformatics prediction and/or modeling of potential protein complexes.

Pharmacological relevance of the non-coenzyme action of thiamin

Thiamin deficiency states affect the brain thiamin level significantly less than that of liver, because compensatory response induces increased thiamin uptake and phosphorylation in brain [48]. Reciprocally, physiological benefits upon thiamin administration are not necessarily accompanied by increased activities of the ThDP-dependent enzymes or ThDP levels in brain [49,36]. Absence of the correlation between positive effects of thiamin administration and brain levels of ThDP or ThDP-dependent enzymatic activities does not allow one to attribute the thiamin effects in patients with neurodegenerative diseases solely to the coenzyme role of ThDP, especially because thiamin or its derivatives may affect functions of other proteins important for neurotransmission and neurodegeneration, such as rapsyn, PARP-1 and interacting with β-amyloid prion. Indeed, traditional explanations, ascribing all the consequences of the thiamin deficiency for neurotransmission and neurodegeneration to the impaired energy production by ThDP-dependent enzymes, are not convincing when thiamin deficiency causes such highly specific and regulated events as, e.g., changed RNA editing of glutamate receptors [14] increased β-secretase activity [15] or altered expression of tight junction proteins and metalloproteinases [16]. In contrast, because both β-amyloid and glutamate receptors were shown to interact with prion [44] which binds thiamin [42,43], changes in these interactions due to insufficient binding of thiamin to prion in thiamin deficiency may well be responsible for perturbed glutamate neurotransmission and β-amyloid accumulation. It is also worth noting that many pharmacological agents are thiazole compounds, but their application overlooks the fact that thiazole heterocycle is a specific part and the degradation product of thiamin. Therefore the thiazole drugs may interact with targets normally binding thiamin or its derivatives. For instance, the drugs which reduce hyperphosphorylated tau-protein in AD mouse models [50], possess structural similarity to thiamin and may therefore mimic or interfere with the pathways of the thiamin non-coenzyme action in synaptic transmission. Especially under conditions of the high-dose thiamin treatment, which is beneficial for patients with neurodegenerative diseases, potential contribution of the non-coenzyme action should not be neglected. As noted elsewhere regarding AdThTP [47], the high dose may elevate not only ThDP, but also the non-coenzyme forms which may thus be also responsible for the therapeutic effects of thiamin. Unraveling the mechanisms of therapeutic action of thiamin compounds beyond the coenzyme ThDP is therefore necessary to create more efficient pharmacological forms and dosage of thiamin.

Acknowledgement

This work was supported by Russian Science Foundation (grant № 14-15-00133 to VB)

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