Vitamins B1, B3 and B6 in Charcot–Marie–Tooth Disease

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The molecular mechanisms of Charcot–Marie–Tooth (CMT) disease, involving impaired vitamin metabolism and/or actions, are considered in light of the potential therapeutic actions of vitamins B1, B3 and B6 in the disease.

vitamin B1 vitamin B6 vitamin B3 pyridoxal-5′-phosphate thiamine diphosphate

1. Introduction

Pharmacological doses of vitamins may be successfully applied to fight neurological diseases, both acquired and genetically determined [1][2][3][4][5]. The goal of this review is to demonstrate how the understanding of the metabolism and action of vitamins in mammals helps to suggest therapies whose timely application saves genetically, nutritionally and/or aging-compromised organisms from progressive damage. A relatively advanced understanding of mammalian metabolism of vitamin B1 (thiamine), vitamin B3 (nicotinamide, nicotinic acid), and vitamin B6 (pyridoxal, pyridoxine and pyridoxamine), added to the well-known mechanisms of the metabolic action of their coenzyme forms, i.e., thiamine diphosphate (ThDP), NAD+, and pyridoxal-5′-phosphate (PLP), underlies the choice of these vitamins to address the review goal. In view of the wide spectrum of neurological disorders induced by impairments in the metabolism of these vitamins or their coenzyme action, the focus of this research is on vitamin B1-, B3- or B6-related disorders manifesting in Charcot–Marie–Tooth (CMT) disease. When diverse cues converge into the similar pathology, exemplified by axonal degeneration in CMT disease, understanding the different molecular mechanisms of the pathology is essential for finding therapies to counteract the cause of the pathology, not only its symptoms.

Common symptoms due to the compromised metabolic action of each of the vitamins may result from their metabolic interplay. First of all, the coenzyme derivatives of vitamins B1, B3 and B6 function in interconnected metabolic nodes. For instance, de novo production of the major neurotransmitters glutamate and gamma-aminobutyric acid (GABA) from glucose requires the participation of ThDP, PLP, and NAD+ (**Figure 1**), exposing their critical and interconnected value for neuronal function.

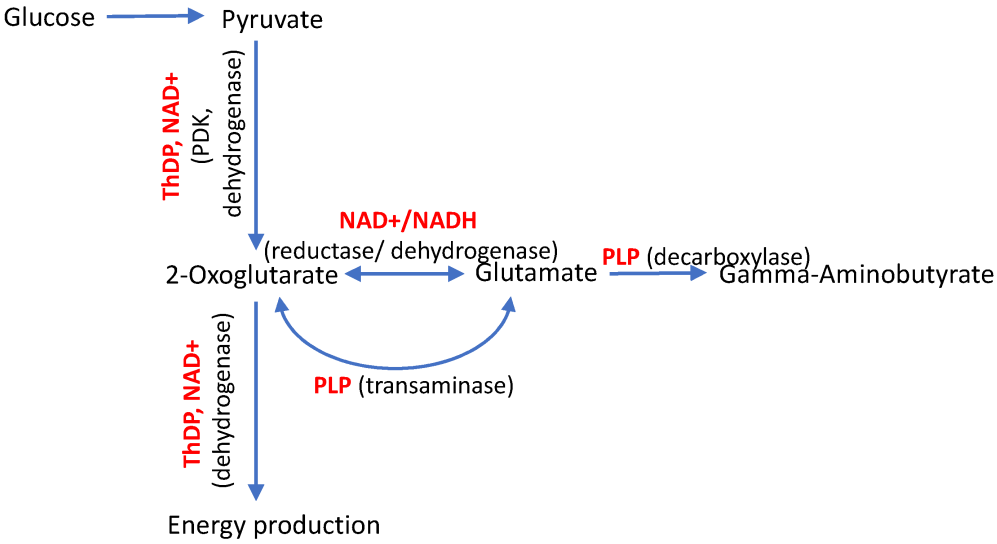

Figure 1. Interplay of natural derivatives of vitamins B1, B3, B6, i.e., thiamine diphosphate (ThDP), oxidized nicotinamide adenine dinucleotide (NAD+), and pyridoxal-5′-phosphate (PLP), correspondingly, in the de novo production of major neurotransmitters glutamate and gamma-aminobutyrate from glucose. The vitamin-dependent enzymes are mentioned in parentheses alongside the type of the catalyzed reactions. PDK stands for pyruvate dehydrogenase kinase, the ThDP-regulated enzyme inactivating the ThDP-dependent pyruvate dehydrogenase through phosphorylation.

Amphibolic metabolite 2-oxoglutarate is generated from glucose in the mitochondrial tricarboxylic acid cycle. The further ThDP-dependent degradation of 2-oxoglutarate results in energy production. Alternatively, 2-oxoglutarate is required for the biosynthesis of glutamate, which occurs through the PLP-dependent transamination or NAD+-dependent reductive amination of 2-oxoglutarate. Glutamate further generates GABA in the PLP-dependent decarboxylation (**Figure 1**). This example demonstrates that perturbed levels of any of the involved vitamin derivatives may adversely affect the metabolic network of the major neurotransmitters. Therefore, different regulatory mechanisms exist to support the stable functioning of the metabolic network upon perturbations in specific reactions. In particular, the enzyme pyridoxal kinase, producing the coenzyme form of vitamin B6, is regulated by phosphorylated forms of vitamin B1 [6]. The interplay of B1, B3, and B6 vitamins in the metabolic pathways essential for neural functions provides a good explanation for the notion that different perturbations in vitamin-dependent processes may converge into axonal degeneration, underlying the neuropathological symptoms of CMT disease. Moreover, exacerbation of the disease symptoms with aging may be contributed by the known age-associated impairments in vitamin status and metabolism [7][8][9][10].

2. General Information on Charcot–Marie–Tooth Disease and Associated Mutations

CMT disease is a group of non-fatal neurological disorders affecting approximately 1 in 2500 people. Despite clinical and genetic heterogeneity, common manifestations of the disease are impairments of the motor and/or sensory peripheral nerves, resulting in muscle weakness and atrophy, accompanied by sensory loss. The neural

cells of patients with this disease cannot support the required electrostimulation due to axonal anomalies in the motor and sensory neurons. Impaired peripheral signaling in CMT disease is generally suggested to be due to de-energization of the axon endings, which is linked to mitochondrial abnormality. Dependent on the primary cause, the two major forms of CMT are the demyelinating form and axonal form [11]. Although the convergent symptoms point to interdependence of the pathological events in different forms of CMT disease, identification of its specific molecular mechanisms is crucial for cause-directed therapies. Yet, in autosomal recessive CMT disease, causal genetic variants are identified only in a quarter of all cases.

Approximately 1000 mutations in 90 different genes are currently known to cause CMT disease, with most of the mutations affecting the cytoskeleton or axonal trafficking [12][13]. Genetic impairments in the mitochondrial proteins represent the most direct pathway to mitochondrial insufficiency associated with CMT disease. The two genes (*DHTKD1*, *PDK3*) encode for the mitochondrial enzymes binding the coenzyme form of vitamin B1 (ThDP), and another gene (*PDXK*) encodes for the producer of the coenzyme form of vitamin B6 (PLP). Mitochondrial metabolism and energy production strongly depend on both the ThDP- and PLP-catalyzed reactions (**Figure 1**).

In addition to mutated genes, a balance between biosynthesis and degradation of a major mitochondrial redox substrate NAD+ (vitamin B3 derivative) has a significant role in axonal degeneration [14][15]. The link between the NAD+ levels and CMT disease is supported by reduced levels of NAD+ in the blood of CMT patients vs. healthy subjects [16]. Thus, the pathogenic mechanisms of CMT disease, arising due to currently known mutations in the ThDP- or PLP-binding enzymes, are considered below, along with the data from animal and cellular models that demonstrate the molecular mechanisms underlying the potential use of vitamins B1, B3, and B6 as therapeutic agents to overcome CMT pathology.

3. CMT Disease upon Mutations of Vitamin-Dependent Enzymes

3.1. Vitamin-B6-Dependent Pyridoxal Kinase

The *PDXK* gene encodes for pyridoxal kinase (PDXK), catalyzing the ATP-dependent phosphorylation of different vitamers of vitamin B6 (pyridoxal, pyridoxin, pyridoxamine) to their phosphorylated forms. The phosphorylated derivative of pyridoxal, PLP, is a coenzyme of a number of enzymes, including those essential for energy production and neurotransmitter metabolism. The enzymes are exemplified in **Figure 1** as transaminases and PLP-dependent decarboxylases.

The variants cause the autosomal recessive CMT disease of 6C type (CMT6C) with primary axonal polyneuropathy and optic atrophy, also called as hereditary motor and sensory neuropathy-type VIC with optic atrophy (HMSN6C) [3]. Distal muscle weakness and atrophy predominantly affecting the lower limbs have an onset in the first decade of life. Optic atrophy and vision loss occur during adulthood.

The substituted amino acids Ala228 and Arg220 are evolutionary conserved residues participating in PDXK interaction with its substrate ATP. Hence, substitutions of these conserved residues impair the substrate binding, resulting in the reduced PDXK activity and low PLP levels observed in the patients. Another homozygous missense mutation in the *PDXK* gene (c.225T>A with the protein substitution Asn75Lys) has been revealed in two children from one family exhibiting symptoms of CMT disease [17]. This substitution decreases the stability of the PDXK dimer and increases protein degradation. As a result, the patient levels of the PDXK activity and PLP are very low.

Oral PLP administration at a dose of 50 mg/kg, known to have none of the neurotoxic effects that are possible with high doses of vitamin B6, increases the levels of PLP in the blood of patients with pathogenic substitutions in PDXK, characterized by impaired production of PLP [3][17]. In CMT disease with the Ala228Thr substitution in PDXK, the PLP replacement scheme has been shown to stably increase PLP levels in patients up to 24 months [3]. Moreover, upon long-term follow-up, an increase in PLP alleviates the symptoms and moderates the progress of CMT disease induced by mutations of *PDXK* gene. The data obtained [3][17] stress the need to screen for potential *PDXK* mutations in patients with autosomal recessive polyneuropathy of early onset, as prompt PLP supplementation may cause long-term improvement in clinical outcomes.

3.2. Vitamin-B1-Dependent Enzymes

Vitamin B1 (thiamine), its natural derivative ThDP (cocarboxylase), and pharmacological forms (benfotiamine, sulbutiamine, etc. [18]) are known to exhibit cardio- and neuroprotective actions under a variety of conditions associated with dysfunctional mitochondria [1][19][20][21]. A potential link between thiamine and the CMT disease symptoms is supported by an outbreak of a peripheral neuropathy similar to CMT disease in 88 male prisoners with hyporeflexia/areflexia of the lower extremities, sensory deficit, and motor weakness. The pathology has been diagnosed along with the observation of thiamine deficiency in 80% of the aforementioned prisoners [22].

Regarding the benefits of thiamine and its known pharmacological forms for treating CMT disease, cases of the disease induced by pathogenic mutations in the genes encoding for mitochondrial enzymes regulated by ThDP are of special interest. These are mutations in the *DHTKD1* and *PDK3* genes encoding the mitochondrial enzymes 2-oxoadipate dehydrogenase (OADH) and the neural-tissue-specific isoenzyme 3 of pyruvate dehydrogenase kinase (PDK3), correspondingly. ThDP is a coenzyme of OADH and an inhibitor of PDK3 [23][24][25]. Remarkably, ThDP is also a coenzyme of the PDK3 target pyruvate dehydrogenase, which is inactivated by PDK3-catalyzed phosphorylation. As the first component of the key mitochondrial pyruvate dehydrogenase complex (PDC) coupling glycolysis to the mitochondrial metabolism, pyruvate dehydrogenase is indispensable for oxidation of the glucose-derived pyruvate in mitochondria (**Figure 1**).

While PDK3-dependent PDC phosphorylation is a well-known regulatory mechanism [26], the role of the OADH-dependent PDC glutarylation is only just emerging [27]. Nevertheless, the finding that OADH is involved in post-translational modifications of PDC in addition to PDK3, is of pathophysiological significance, as excessive protein glutarylation has been observed in a number of pathological states [28].

3.2.1. Isoenzyme 3 of Kinase of the ThDP-Dependent Pyruvate Dehydrogenase

Mutation c.G473>A in the *PDK3* gene causes the substitution Arg158His in PDK3, representing the genetic cause of an X-linked dominant form of axonal CMT disease (CMTX6) (OMIM 300905) [12][29][30]. Males are more severely affected by this mutation than females. The symptoms onset occurs within the first 13 years, when the muscle weakness and atrophy, predominantly in lower limbs, and sensory deficits are detected. Some of the affected men have moderate sensorineural hearing loss and perturbed auditory brainstem response.

The substitution Arg158His leads to a hyper-active PDK3 exhibiting an increased affinity to PDC, compared to the wild-type enzyme. As a result, higher levels of phosphorylation and inactivation of cellular PDC are observed in patients carrying this mutation [30]. The metabolic characteristics of fibroblasts and iPSC-derived motor neurons of the patients reveal failures in energy production and mitochondrial function. In vivo models wherein the Arg158His-substituted PDK3 ortholog, known as PDHK2 in *C. elegans*, is knocked-in, or the wild-type and mutated PDK3s are overexpressed in the GABA-ergic motor neurons, recapitulate deficits in mitochondrial function and synaptic neurotransmission, as observed in the cellular studies [12]. Additionally, the models reveal characteristics of CMT disease, such as locomotion defects and signs of progressive neurodegeneration.

ThDP is known to inhibit kinases of pyruvate dehydrogenase [23][24][25]. Hence, patients with CMT disease induced by hyperactive PDK3 may benefit from administration of the PDK3 inhibitor ThDP, which is well-known in medicine and pharmacology as cocarboxylase. Pharmacological lipophilic forms of thiamine (vitamin B1), such as sulbutiamine (enerion) and benfotiamine, are also widely available. Remarkably, ThDP inhibition of PDK3 would increase the activity of pyruvate dehydrogenase by decreasing the enzyme phosphorylation level. Simultaneously, as a coenzyme of pyruvate dehydrogenase, ThDP may activate the PDC-catalyzed oxidation of the glycolytic product pyruvate via an independent mechanism, such as the saturation of the pyruvate dehydrogenase with its coenzyme. As a result, the thiamine or ThDP administration may counteract the hyperactivity of the Arg158His-substituted PDK3 by inhibiting PDK3 and activating PDC, potentially relieving the CMT disease caused by this mutation. This mechanistic knowledge calls for a clinical evaluation of the therapeutic effect of vitamin B1 or its derivatives in CMT patients with the hyperactive PDK3.

3.2.2. Molecular Mechanisms of CMT Disease Caused by Mutations in the DHTKD1-Encoded ThDP-Dependent 2-Oxoadipate Dehydrogenase

The axonal type of CMT disease type 2Q (OMIM 615025) is described upon heterozygous loss-of-function mutation of the *DHTKD1* gene encoding for the mitochondrial ThDP-dependent OADH [31]. The mutation c.1455T>G in exon 8 of the *DHTKD1* gene causes preterm termination of the transcription at the Tyr485 codon, and a 2-fold decrease in the OADH mRNA. The resulting autosomal dominant form of CMT disease is characterized by muscle atrophy, predominant weakness of the lower limbs, decreased or absent deep tendon reflex, and mild to moderate sensory impairment. The symptom onset is detected from 13 to 25 years.

Mice models of homozygous knockout of the *DHTKD1* gene mimic the CMT disease phenotype, demonstrating the anatomic and functional features of peripheral neuropathy with characteristic perturbations of the motor and

sensory functions, axonal degeneration, and muscle atrophy. The phenotype is accompanied by serious metabolic abnormalities, with significant increases in the urine levels of 2-oxoadipate and its transamination product 2-aminoadipate [32].

Pathogenic homozygous *DHTKD1* mutations are associated with strongly increased levels of the OADH substrate 2-oxoadipate and its derivatives (2-aminoadipate, 2-hydroxyadipate), causing severe neurological manifestations, delayed development, chronic diseases of respiratory pathways, and early muscle atrophy [33][34][35]. Nevertheless, in some mutants, clinical manifestations are absent, even when biochemical parameters are perturbed [34][35].

The pathogenicity of heterozygous mutations in the *DHTKD1* gene varies. The mutations may be associated with neuropathies, such as CMT disease and similar states, with autoimmune disease, such as eosinophilic esophagitis, or with epilepsy, but often the same mutations may be present in asymptomatic persons [31][36][37][38]. Most of the nucleotide substitutions in the *DHTKD1* gene are asympthomatic [39]. Thus, understanding molecular basis of pathophysiological impact of the *DHTKD1*-encoded OADH is not straightforward.

The current level of characterization of the structure–function relationship in the OADH molecule allows one to predict the pathogenicity of the amino acid substitutions in the enzyme active site and protein–protein interfaces. Structures of recombinant OADH [39][40] and homology modelling of the enzyme complexes with its ligands [41][42] reveal the impact of OADH mutations in the active site and dimeric interface of the enzyme on the enzyme-catalyzed reaction. Besides, the protein residues involved in heterologous interactions upon formation of the OADH multienzyme complex, where OADH catalyzes oxidative decarboxylation of 2-oxoadipate with generation of glutarylCoA and NADH, are also characterized [43][44][45]. This knowledge enables predictions of functional impairments due to mutations affecting the complex formation. Nevertheless, several considerations are important to note, regarding the varied pathophysiological impact of the same DHTKD1 mutations in different carriers of a mutation. First, the catalytic function of OADH is redundant, and could well be substituted by an ubiquitously expressed OADH isoenzyme, 2-oxoglutarate dehydrogenase (OGDH). In vitro, OGDH catalyzes oxidative decarboxylation of 2-oxoadipate at a rate of up to 50% of that of oxidative decarboxylation of 2-oxoglutarate, with OGDH expression usually exceeding that of OADH [46]. Second, in animal tissues, OADH undergoes post-translational modifications strongly affecting the enzyme structure, compared to that of the characterized recombinant enzyme, which may correspond to the existence of an as yet unidentified enzyme function [47]. Third, the biochemical effects of OADH mutations, i.e., increases in the 2-oxo/aminoadipate levels, are not necessarily accompanied by clinical symptoms [34]. These considerations suggest that the (patho)physiological impact of OADH relies on the OADH-specific interplay with other proteins/pathways, rather than solely on OADH catalytic function.

This assumption is supported by the data on the most characterized associations of OADH with insulin resistance, obesity and type II diabetes. The data not only reveal the significance of genetic background in the biological impact of OADH, but also suggest that perturbed glucose metabolism is a molecular mechanism underlying OADH-associated neurological disorders. Indeed, increased 2-oxoadipate and/or 2-aminoadipate levels in the mice knockouts of *DHTKD1* [32][48][49] cause an insulin resistance phenotype [32]. Liver expression of *DHTKD1* is the

major regulator of the level of 2-aminoadipate, the transamination sibling of the OADH substrate 2-oxoglutarate, in serum [50]. Dependent on external (diet) and genetic (different alleles) factors, *DHTKD1* gene expression also correlates with levels of glucose and cholesterol, and the diabetic status [50]. In the blood plasma of humans and mice, glucose levels are negatively correlated with those of 2-aminoadipate, while the levels of 2-aminoadipate and insulin correlate positively [51]. When β-cells of the pancreas are treated with 2-aminoadipate, more insulin is secreted, corresponding with increased insulin secretion upon the accumulation of 2-aminoadipate in the pancreas, as observed in mice on a high-fat diet [51]. At the same time, mice knockouts of the *Csf2* gene (controlling the function of granulocytes and macrophages) are obese without diabetic symptoms. Remarkably, these mice exhibit increased expression of *DHTKD1* and decreased 2-aminoadipate levels compared to wild-type mice [52]. *DHTKD1* expression is also increased by a natural compound mangiferin, preventing obesity [53]. Vitamin B1 (thiamine), which is a precursor of the OADH coenzyme ThDP, upregulates OADH activity in the rat cerebellum [54].

Thus, relatively low expression of *DHTKD1* may be an early indicator of obesity and type II diabetes, while increased expression of *DHTKD1* is associated with clinical improvement of such states [55]. Pharmacological regulation (e.g., mangiferin, vitamin B1) or genetic factors (exemplified by knockout of the *Csf2* gene) may increase *DHTKD* expression. Compensating for functional impairments in the OADH mutants, this conditional increase in *DHTKD* expression may contribute to the heterogeneity of the mutant *DHTKD1* phenotypes. The available data thus imply that pharmacological upregulation of OADH expression and/or activity via administration of vitamin B1 may be of therapeutic value.

If phenotypic manifestations of the *DHTKD1* mutations, particularly in CMT disease, depend on the function of other genes, a question arises what these other genes are. To answer this question, a closer look at the metabolic pathways potentially affected by OADH function is required (**Figure 2**).

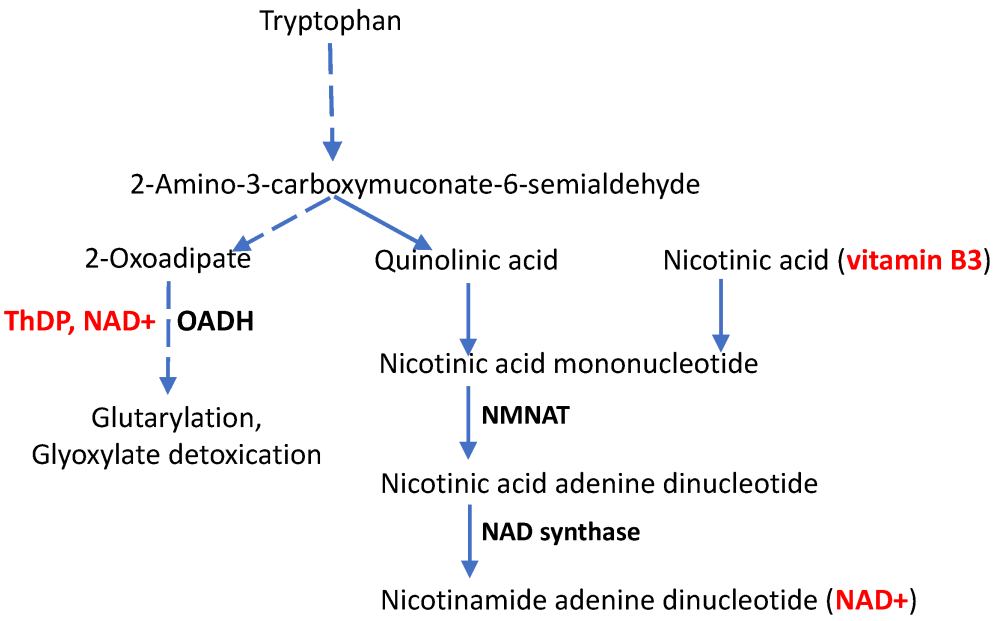

Figure 2. Participation of *DHTKD1*-encoded 2-oxoadipate dehydrogenase (OADH) in the tryptophan catabolism pathway, alternative to de novo NAD+ biosynthesis from tryptophan. Dashed lines represent multistep processes,

the vitamins and their natural derivatives are shown in bold red, and the enzymes mentioned in the text are shown in bold black text. Nicotinamide/nicotinic acid mononucleotide adenylyl transferase (NMNAT) and NAD synthase catalyze the indicated steps of NAD+ biosynthesis.

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