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NARRATIVE REVIEW

Biochemical Mechanisms of Thiamine Pyrophosphate and Their Relevance to Neurology: Recent Advances, Comparisons and Limitations

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ABSTRACT

Background: Thiamine pyrophosphate (also called thiamine diphosphate, ThDP or TPP) is the active form of vitamin B_1 and an obligatory cofactor for enzymes at the junction of glycolysis, the tricarboxylic acid (TCA) cycle and the pentose phosphate pathway. Neurons depend heavily on these routes, which makes the nervous system especially vulnerable to disturbed thiamine handling.

Objective: To review the chemical and enzymatic mechanism of ThDP, compare its principal enzymes, transport routes and thiamine forms, and appraise its advantages and limitations in neurology.

Approach: Narrative review of selected primary studies, systematic reviews, guidelines and structural papers. It is not a systematic review; no exhaustive database search or formal risk-of-bias assessment was performed. Every cited source was checked against its bibliographic record or abstract.

Findings: Catalysis depends on a thiazolium C2 ylide/carbene, covalent substrate adducts and an enamine (C2α-carbanion) intermediate, with the 4′-aminopyrimidine ring acting as an intramolecular proton relay. Recent work refines the cofactor states, reveals unusual reactions and superassemblies, and resolves the native architecture of the mammalian 2-oxoglutarate dehydrogenase complex. In neurology, thiamine is a safe, inexpensive and effective treatment for Wernicke encephalopathy and for several inherited transport and metabolism disorders, while benfotiamine shows potential, but not yet proven, benefit in early Alzheimer disease.

Conclusions: Principal limitations are compartmentalised thiamine pools, a poor correlation between blood status and brain status, limited brain delivery of prodrugs and small, early-phase clinical evidence. Brain-targeted delivery, better biomarkers and adequately powered trials are priorities.

Keywords: Thiamine pyrophosphate; thiamine diphosphate; vitamin B_1; enzyme mechanism; 2-oxoglutarate dehydrogenase; Wernicke encephalopathy; SLC19A3; benfotiamine; Alzheimer disease.

1. Introduction

Thiamine (vitamin B_1) is converted in cells to thiamine diphosphate (ThDP, also written TPP), the coenzyme of enzymes that cleave and form carbon–carbon bonds next to a carbonyl group [1,2]. Because the key ThDP enzymes link glucose-derived pyruvate to the TCA cycle, supply the TCA cycle with succinyl-CoA and feed the pentose phosphate pathway, a shortage of the cofactor impairs energy and biosynthetic metabolism [6]. The brain combines high energy demand with limited reserves, so neurological disease is a leading manifestation of thiamine failure, from Wernicke encephalopathy to inherited disorders of thiamine transport [7,8].

This narrative review integrates: (i). the chemical mechanism of ThDP catalysis; (ii). comparisons among ThDP enzymes, transporters and thiamine forms; and (iii). the advantages and limitations of

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thiamine-based approaches in neurology. It is not a systematic review: no exhaustive database search, risk-of-bias appraisal or pooling was undertaken. Sources were selected to represent foundational mechanistic work, recent structural and computational advances, genetic and clinical neurology, and translational trials; each was verified against its bibliographic record or abstract. Key milestones are summarised in Figure 1.

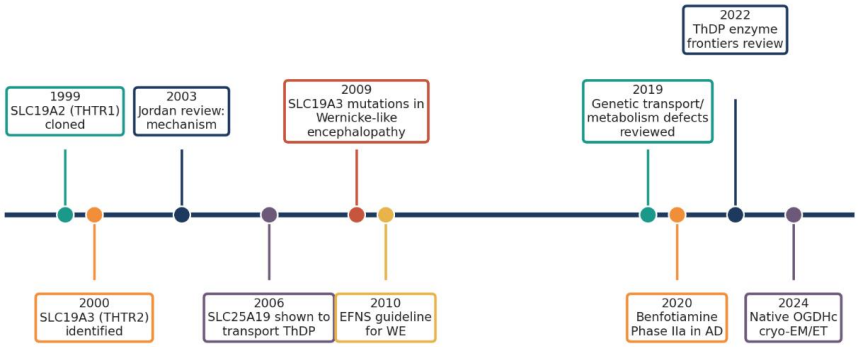


Figure 1. Selected milestones in thiamine pyrophosphate biochemistry and neurology [1,5,7–10,12,13]. Dates follow the cited sources.

2. Chemical mechanism of ThDP catalysis

2.1 Cofactor architecture and activation

ThDP consists of a 4′-aminopyrimidine ring, a thiazolium ring and a diphosphate tail that is anchored in the active site through a protein-bound magnesium ion (Figure 2A). Its function is to greatly increase the acidity of two carbon acids by stabilising their conjugate bases: The C2 ylide/carbene (C2-carbanion) of the thiazolium ring, and, once the substrate has bound, the C2α-carbanion/enamine [2]. A major advance in the field was the recognition that the 4′-aminopyrimidine ring is not a spectator: the current view is that both aromatic rings contribute to catalysis, probably through an intramolecular proton transfer that initiates the reactions, an ability that makes ThDP almost unique among coenzymes [1].

2.2 The catalytic cycle

In a typical 2-oxo acid decarboxylation, deprotonation of C2 generates the ylide, which attacks the substrate carbonyl to form a covalent adduct; loss of CO_2 then gives the enamine, which is processed according to the enzyme class (Figure 2B, Table 1) [1,2]. Several ThDP-bound intermediates have now been characterised by X-ray crystallography, rapid chemical quench with NMR detection, solid-state NMR and circular dichroism, including the ionisation and tautomeric states of the aminopyrimidine ring [2].

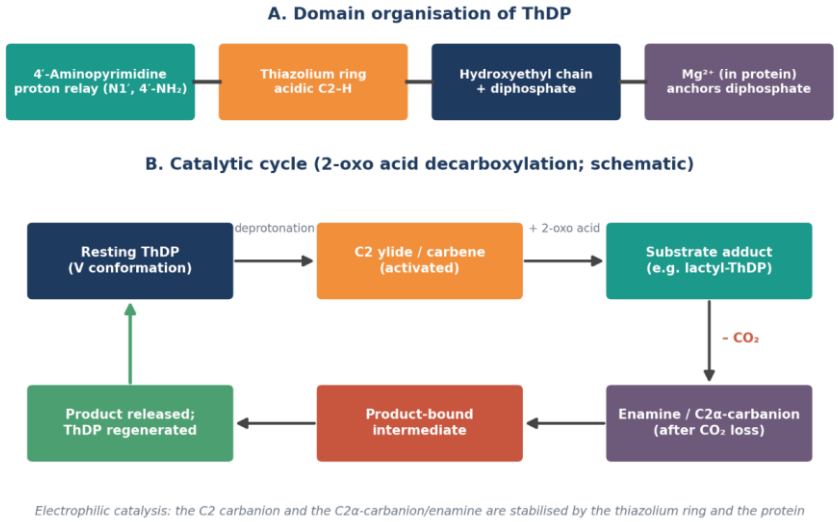


Figure 2. Schematic of ThDP. (A) Functional domains of the cofactor. (B) Simplified catalytic cycle for 2-oxo acid decarboxylation; intermediates are generalised from refs. [1,2].

Table 1. Principal mechanistic steps of ThDP-dependent catalysis.

Step	Event	Chemical species and key features	Sources
1	Cofactor activation	Deprotonation of thiazolium C2, assisted by the 4′-aminopyrimidine ring, gives the C2 ylide/carbene	[1,2]
2	Substrate addition	Ylide attacks the substrate carbonyl, forming a covalent ThDP–substrate adduct (e.g. lactyl-ThDP)	[1,2]
3	C–C bond cleavage	Decarboxylation yields the enamine/C2α-carbanion, a stabilised acyl-anion equivalent	[1,2]
4	Fate of the enamine	Protonation (decarboxylases), carboligation (transketolase-type) or transfer to the lipoyl group of E2 (2-oxo acid dehydrogenase complexes)	[1,3]
5	Release and regeneration	Product dissociates; ThDP returns to the resting state	[1,2]

2.3 Recent mechanistic and structural advances

Recent reviews highlight "unusual" reactions and reaction intermediates that illustrate the chemical versatility of the cofactor, the structural basis of cooperativity between active sites, new insight into selected enzymes, and the discovery of "superassemblies" such as those of acetohydroxy acid synthase [3]. Quantum-chemical work on benzoylformate decarboxylase predicted that, besides the catalytically competent forms, the cofactor can adopt a surprisingly stable inactive tricyclic state; binding of the substrate favoured ylide formation but stabilised the tricyclic state even more, with implications for reaction kinetics and for the use of unnatural substrates [4]. Characteristic spectroscopic signatures of cofactor states have been observed in more than ten ThDP enzymes [4].

For the neurologically important 2-oxoglutarate dehydrogenase complex (OGDHc), a 2024 study combined cryo-electron microscopy, cryo-electron tomography and subtomogram averaging on the native porcine complex. It resolved the E2o cubic core of eight homotrimers at 3.3 Å and showed that the peripheral E1o and E3 subunits, although variable in distribution, follow a degree of regularity in position and orientation [5].

3. Comparison of principal ThDP-dependent enzymes

Despite sharing the cofactor chemistry, ThDP enzymes differ in the fate of the enamine intermediate, in cellular compartment and in vulnerability to thiamine depletion (Table 2). The mitochondrial dehydrogenase complexes (E1–E2–E3 assemblies) couple decarboxylation to acyl transfer and NADH production, whereas transketolase operates in the cytosol of the pentose phosphate pathway [3,6]. Thiamine deficiency reduces the activity of ThDP enzymes, and genetic loss of the mitochondrial ThDP carrier lowers both pyruvate dehydrogenase and 2-oxoglutarate dehydrogenase activities [10].

Table 2. Comparison of principal ThDP-dependent enzymes.

Enzyme	Location / pathway	ThDP-dependent step	Neurological relevance
Pyruvate dehydrogenase complex (PDHC)	Mitochondria; links glycolysis to the TCA cycle	E1 decarboxylates pyruvate; acyl group passes to E2 and onward to acetyl-CoA [6]	Activity reduced in cells lacking mitochondrial ThDP [10]
2-Oxoglutarate dehydrogenase complex (OGDHc)	Mitochondria; rate-limiting TCA step [5]	E1o decarboxylates 2-oxoglutarate to the enamine; succinyl group passes to E2o [3]	ThDP-enzyme activities decline in blood and brain in Alzheimer disease [13]; reduced in SLC25A19-deficient cells [10]
Branched-chain 2-oxo acid dehydrogenase (BCKDH)	Mitochondria; branched-chain amino acid catabolism	Decarboxylation of branched-chain 2-oxo acids by the same E1–E2–E3 logic [3]	Not examined in the studies reviewed here
Transketolase	Cytosol; pentose phosphate pathway [6]	ThDP-dependent carbon–carbon bond transfer (carboligation-type) [1]	Supports NADPH and ribose supply; depends on cytosolic ThDP [6,14]

In Table 2 "not examined" indicates absence from the sources reviewed, not absence of relevance.

4. Thiamine uptake, activation and compartmentation

Thiamine enters cells through the transporters THTR1 (SLC19A2) and THTR2 (SLC19A3); further transporters, including SLC44A4 in the colon and organic cation transporters, have since been identified [7]. Inside the cell, thiamine is phosphorylated to ThDP by thiamine pyrophosphokinase 1 (TPK1) and to thiamine triphosphate by TDPK, and the phosphates can be removed again by ACPP and THTPA [6]. ThDP must then reach the mitochondrial matrix: the mitochondrial carrier SLC25A19 transports ThDP, and its knockout in mice depletes mitochondrial ThDP and lowers PDH and KGDH activities, with embryonic lethality and central nervous system malformations [10]. These steps are summarised in Figure 3.

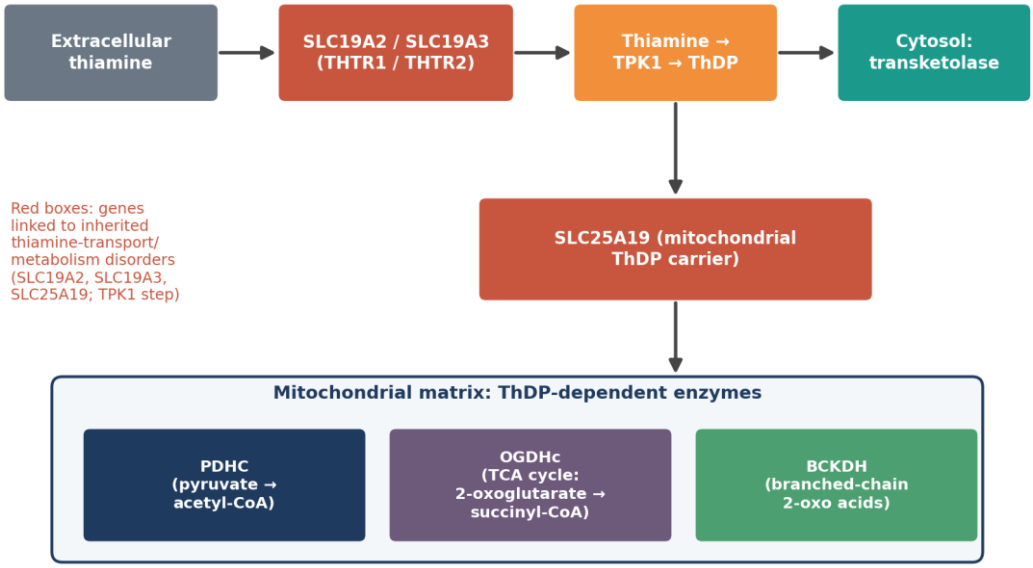


Figure 3. Cellular thiamine handling and ThDP-dependent enzymes. Steps highlighted in red are linked to inherited disorders [6,8,10].

Four genetic defects of thiamine transport and metabolism have been described: SLC19A2 dysfunction causes diabetes mellitus, megaloblastic anaemia and sensorineural hearing loss, whereas SLC19A3, SLC25A19 and TPK1 disorders cause recurrent encephalopathy, basal ganglia necrosis, generalised dystonia, severe disability and early death [8] (Table 3). In the original description of SLC19A3 mutations in Wernicke-like encephalopathy, high expression of the gene in the thalamus was proposed to explain selective thalamic lesions on MRI [9].

Table 3. Inherited disorders of thiamine transport and metabolism.

Gene	Protein / role	Clinical features	Thiamine response
SLC19A2	THTR1; thiamine uptake	Diabetes mellitus, megaloblastic anaemia, sensorineural hearing loss [8]	Thiamine improves diabetes and anaemia control [8]
SLC19A3	THTR2; thiamine uptake, expressed in brain	Recurrent encephalopathy, basal ganglia necrosis, dystonia; profound fall of free thiamine in CSF [8,9]	Improved outcome and survival in a significant number of patients [8]
SLC25A19	Mitochondrial ThDP carrier [10]	Bilateral striatal degeneration and progressive polyneuropathy with fever onset (THMD4) [11]	Clinical stabilisation in single cases [8]
TPK1	Converts thiamine to ThDP [6]	Recurrent encephalopathy, basal ganglia necrosis; low ThDP in blood and muscle [8]	Clinical stabilisation in single cases [8]

Table 3 summarises ref. [8], with supporting detail from refs. [6,9–11].

5. Neurological relevance and advantages

5.1 Wernicke encephalopathy

Thiamine deficiency is traditionally divided into Wernicke–Korsakoff syndrome and beriberi [7]. Wernicke encephalopathy (WE) is preventable and treatable but is often undiagnosed during life [12]. The EFNS guideline recommends that thiamine be given for suspected or manifest WE, before any carbohydrate, at 200 mg three times daily, preferably intravenously (Level C); that overall safety is very good (Level B); that MRI supports the diagnosis; and that parenteral thiamine be given to all at-risk patients admitted to the emergency room (good practice point) [12] (Figure 4). Among the strengths of this approach are low toxicity, low cost and a rapid, mechanism-based rationale.

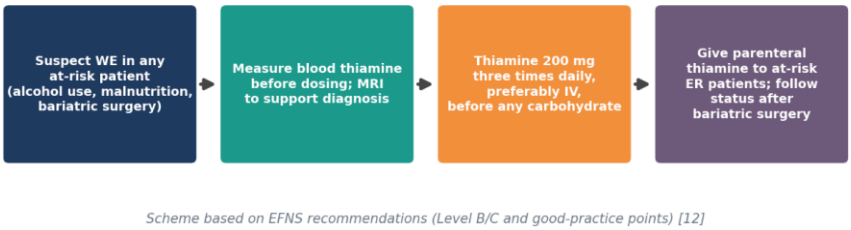


Figure 4. Management scheme for suspected Wernicke encephalopathy, summarising the EFNS recommendations [12].

5.2 Inherited disorders

Genetic disorders show the clearest causal link between ThDP supply and neurological disease, and also the clearest therapeutic payoff: thiamine improves clinical outcome and survival in a significant number of SLC19A3 patients and prevents further metabolic crises, and supplementation normalises free thiamine in cerebrospinal fluid [8]. Free thiamine in CSF and fibroblasts (SLC19A3) and ThDP in blood and muscle (TPK1) serve as biomarkers [8]. In SLC25A19 and TPK1 defects, benefit has so far been reported only in single cases [8].

5.3 Alzheimer disease and benfotiamine

ThDP-dependent enzymes regulate key steps in brain glucose metabolism, and their activities decline in the blood and brain of patients with Alzheimer disease (AD) [13]. Reduction of brain ThDP correlates strongly with glucose hypometabolism in AD, whereas amyloid deposition does not [15]. In a randomised, placebo-controlled Phase IIa trial, 70 participants with amnestic mild cognitive impairment or mild AD dementia received benfotiamine (34) or placebo (36) for twelve months; treatment was safe, and the authors concluded it was potentially efficacious [13]. An independent trial summary notes, however, that the primary ADAS-Cog endpoint was not met: the benfotiamine group declined 43% less, but this fell short of statistical significance [16]. These findings are hypothesis-generating (Table 4).

Table 4. Neurological conditions in which ThDP availability is implicated.

Condition	Mechanistic link	Therapeutic evidence	Status and limits
Wernicke encephalopathy	Dietary or absorptive thiamine deficiency; impaired ThDP enzymes [7]	IV thiamine 200 mg three times daily recommended [12]	Established; guideline strength Level B/C [12]
SLC19A3-related disease	Defective neuronal thiamine uptake [8,9]	Thiamine improves outcome in many patients [8]	Rare; registry and trial data limited [8]
SLC25A19 / TPK1 disorders	Failed mitochondrial import or synthesis of ThDP [8,10]	Stabilisation in single cases [8]	Case-level evidence only [8]
Alzheimer disease	Reduced ThDP-enzyme activity and brain ThDP [13,15]	Benfotiamine 600 mg/day, 12 months: safe; primary endpoint not significant [13,16]	Pilot; replication needed

Table 4 is the evidence strength as stated in the cited sources.

6. Comparison of thiamine forms and delivery

Conventional thiamine is the standard agent for WE [12]. Benfotiamine is a synthetic, fat-soluble precursor with high bioavailability, used in diabetic neuropathy at 150–300 mg per day [16]. In animal models of amyloid plaques, benfotiamine and fursultiamine raised blood thiamine about 150-fold and 50-fold respectively, but brain effects were far smaller: brain thiamine doubled while brain TMP and ThDP did not change; in a tau model brain thiamine rose only about 20%, and in a streptozotocin model brain ThDP rose about 50% [14] (Figure 5, Table 5). Delivery of thiamine to the brain is therefore a central design problem.

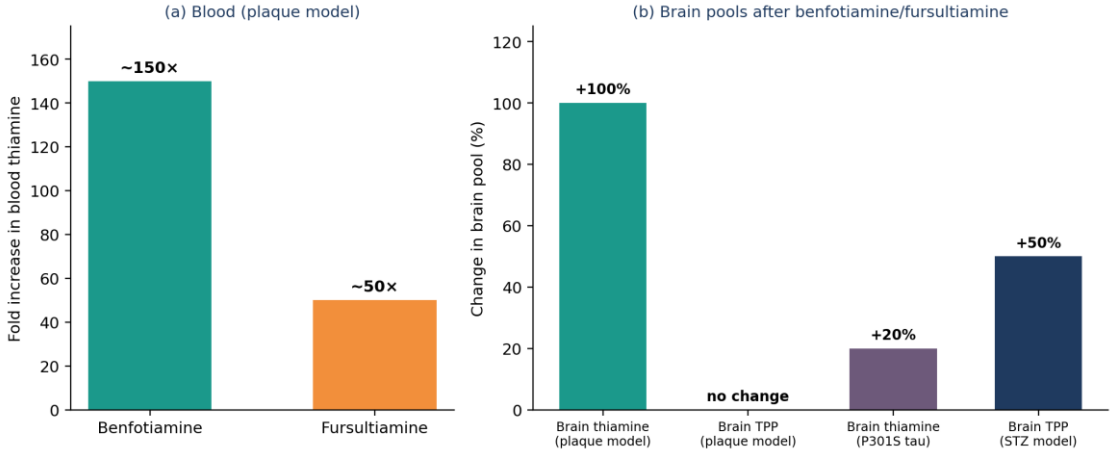


Figure 5. Fold increase in blood thiamine and percentage change in brain pools after benfotiamine or fursultiamine in mouse models. Approximate values as reported in ref. [14].

Table 5. Comparison of thiamine forms.

Form	Properties	Evidence in neurology	Sources
Thiamine (water-soluble)	Standard clinical form; IV route preferred in WE	EFNS-recommended in suspected WE; very good safety	[12]
Benfotiamine	Fat-soluble synthetic precursor; high bioavailability	Phase IIa in early AD; blood thiamine ~150× in plaque model	[13,14,16]
Fursultiamine	Thiamine prodrug	Blood thiamine ~50× in plaque model; brain ThDP unchanged	[14]

Table 5 summarises cited data; no head-to-head clinical comparison is available in the sources reviewed.

7. Complexity and limitations

Several layers of complexity limit translation from biochemistry to therapy (Table 6). Thiamine participates in processes in the cytosol, mitochondria and peroxisomes [8], so a single blood measurement cannot capture compartment-specific ThDP. Multiple conditions can alter thiamine transport to the brain, or its use or mobilisation within and between cellular compartments, without changing blood thiamine status [14]. Structurally, cryo-EM analysis of native OGDHc shows heterogeneity in peripheral subunit distribution [5], and computational work shows that cofactor states beyond the catalytic cycle can influence kinetics [4]. Clinically, the best evidence comes from WE guidance graded Level B/C [12] and for small genetic cohorts [8], while the AD evidence rests on one pilot trial [13,16] and on correlative biochemical data [15], which cannot establish causation.

Table 6. Principal complexities and limitations.

Domain	Complexity	Implication for neurology
Compartmentation	Thiamine acts in cytosol, mitochondria and peroxisomes [8]; ThDP must cross SLC25A19 [10]	Whole-blood status may not reflect brain mitochondrial ThDP [14]
Brain delivery	Large blood increases with prodrugs but modest brain increases [14]	Dose–response in brain remains uncertain
Evidence quality	WE guideline Level B/C [12]; AD pilot, n = 70, primary endpoint not significant [13,16]	Conclusions must be provisional
Genetic heterogeneity	Four distinct genetic defects with overlapping phenotypes [8]	Genetic confirmation and biomarkers needed; benefit unproven in SLC25A19/TPK1 [8]
Structural and mechanistic complexity	Heterogeneous native OGDHc [5]; cofactor tricyclic state [4]	Enzyme-specific inhibitors or activators are hard to design
Causality	ThDP loss correlates with hypometabolism in AD, whereas amyloid does not [15]	Association does not prove that restoring ThDP alters disease course

Table 6 Review limitations: The narrative design, selective sources and reliance on abstracts and bibliographic records for verification may omit relevant studies.

8. Future directions

Priorities include brain-targeted thiamine delivery systems, validated biomarkers of compartment-specific ThDP, adequately powered randomised trials in AD and in genetic disorders with registries, and continued structural work on native ThDP enzyme assemblies such as OGDHc [5,14]. Better mechanistic models of cofactor states [3,4] may also help to design selective modulators of individual ThDP enzymes.

9. Conclusions

ThDP catalysis rests on a distinctive chemistry in which a thiazolium ylide, covalent adducts, an enamine intermediate and an intramolecular proton relay cooperate with the protein environment. In neurology, restoring ThDP supply is an inexpensive and safe intervention of proven value in Wernicke encephalopathy and in selected inherited disorders, and a promising but unproven strategy in Alzheimer disease. Compartmentalisation, limited brain delivery and modest clinical evidence define the limits of current knowledge.

Declarations

1. Use of Artificial Intelligence (AI) Tools: AI-assisted tools were used during the preparation of this manuscript to support literature organisation, development of the manuscript structure, language refinement and improvement of scientific presentation. These tools assisted in organising biochemical concepts, comparing published findings and improving the clarity and readability of the text. The authors critically reviewed and edited the AI-assisted content of the manuscript.

2. Funding Declaration: The authors received no specific financial support, research grants or external funding from governmental, commercial, industrial or non-governmental organisations for the preparation of this manuscript.

3. Conflict of Interest: The authors declare that they have no financial, personal, professional or institutional conflicts of interest that could have influenced the content, interpretation or conclusions presented in this review.

4. Ethical Approval: Ethical approval was not required for this study because it is a narrative review based on previously published scientific literature and publicly available information. No experiments involving human participants or laboratory animals were conducted as part of this work.

5. Informed Consent: Not applicable. This manuscript does not involve the recruitment of human participants, collection of personal information or reporting of identifiable patient data.

6. Data Availability Statement: No new experimental datasets were generated or analysed during the preparation of this review. The scientific information discussed is derived from previously published research articles, review papers, biochemical studies, clinical literature and other relevant scientific sources.
7. Author Contributions: The authors contributed to the conceptualisation, literature review, collection and organisation of scientific information, biochemical interpretation, comparative analysis.
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The authors also acknowledge the importance of published biochemical, experimental and clinical research exploring thiamine deficiency, neurological manifestations, therapeutic approaches and the limitations of current evidence. These scientific contributions have provided the foundation for the comparative analysis and critical discussion presented in this narrative review.

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