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Review

How does Thiamine Deficiency cause the Wernicke-Korsakoff Syndrome?

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Abstract

Wernicke-Korsakoff syndrome (WKS) is caused by thiamine deficiency usually due to alcoholism and malnutrition. Decreased activity of thiamine pyrophosphate (TPP)-dependent transketolase (TK) has been regarded as one of the most likely pathogenesis of WKS. TK is an enzyme involved in the non-oxidative phase of the pentose phosphate pathway (PPP) and responds to demands for nicotinamide adenine dinucleotide phosphate (NADPH) essential for lipogenesis in oligodendrocytes. Demyelination has been considered to be a primary event in the development of WKS and caused by impairments of myelin formation due to reduced TK activity. However, the PPP-associated enzymopathies such as deficiencies of glucose 6-phosphate dehydrogenase, transaldolase, and ribose 5-phosphate (R5P) isomerase imply significant roles of the PPP in meeting demands of the brain for R5P as a donor of purine nucleotides. This article reviews the pathophysiology of WKS in terms of the PPP involved in generation of R5P and NADPH.

Keywords: wernicke-korsakoff syndrome, thiamine, transketolase, the pentose phosphate pathway, ribose 5-phosphate, nicotinamide adenine dinucleotide phosphate

Introduction

Glucose is a major source of adenosine triphosphate (ATP), a common energy currency for all brain cells. A primary mechanism for the production of ATP is attributed to anaerobic glycolysis and the aerobic processes including the tricarboxylic acid (TCA) cycle and mitochondrial oxidative phosphorylation (OXPHOS). The biochemical process of glucose oxidation is regulated by various enzyme reactions in response to ATP demands [1]. Some of the reactions require vitamins as an essential cofactor to exert their catalytic actions. Thiamine (vitamin B_1) is converted to its active form, thiamine pyrophosphate (TPP), and subsequently serves as a coenzyme of several enzymes related to glucose metabolism, such as transketolase (TK), pyruvate dehydrogenase complex (PDHC), and α-ketoglutarate dehydrogenase (αKGDH) [2, 3]. Insufficient intake of thiamine can reduce the activity of PDHC and αKGDH belonging to the TCA cycle and significantly affect aerobic glycolysis, consequently leading to energy compromise along with lactic acidosis, which can cause profound impairment of biological functions [3]. Regarding the brain, Wernicke encephalopathy (WE) is caused by thiamine deficiency, which is characterized by clinical signs such as delirium, confusion, significant spatial and temporal disorientation, memory impairment, ataxia, nystagmus, and ophthalmoplegia [4, 5]. Although WE is treatable with adequate replenishment of thiamine, prolonged insufficiency of thiamine can cause significant sequela, such as Korsakoff's syndrome (KS), which is characterized by fixed impairment of memory functions, including lack of insight, anterograde amnesia, retrograde amnesia, and confabulation [3, 5, 6]. Whether KS can develop without WE remains controversial [3, 5, 6]. A patient who developed KS along with pellagra due to chronic undernourishment without having apparent history of chronic alcoholism or episodes suggestive of WE was reported in our previous study [7]. Uncertainty as to whether WE precedes KS might be explained by the fact that clinical diagnosis of WE is very difficult and therefore often missed [6], but the case showed that abnormalities of the brain energy metabolism resulting from malnutrition could induce critical damages to the brain's executive functions.

Hypothesis of the Pathogenesis

To clarify the pathological changes in the Wernicke-Korsakoff syndrome (WKS), many investigators have focused on TK, PDHC, and αKGDH. Among them, TK has been identified as the most relevant pathogenesis of WKS [5, 8]. TK catalyzes two (the first and last) of the three steps in the non-oxidative phase of the pentose phosphate pathway (PPP); 1) the reversible conversion of ribose 5-phosphate (R5P) and xylulose 5-phosphate (X5P) into sedoheptulose 7-phosphate (S7P) and glyceraldehyde 3-phosphate (GAP), and 2) the reversible conversion of erythrose 4-phosphate (E4P) and X5P into fructose 6-phosphate (F6P) and GAP [9]. Since all non-oxidative reactions are reversible, they can provide R5P from GAP and F6P in the absence of the oxidative phase when more nucleotides and nucleic acids are required. Conversely, when a need for nicotinamide adenine dinucleotide phosphate (NADPH) is greater than for R5P, ribulose 5-phosphate is converted into the glycolysis intermediates such as GAP and F6P, which can be used to generate G6P *via* the process of gluconeogenesis [9]. Whether the resultant G6P enters the PPP is dependent on the activity of glucose 6-phosphate dehydrogenase (G6PD), the regulatory enzyme in the oxidative phase of the PPP and responsible for generation of NADPH [9]. For example, when biosynthetic reactions including lipogenesis require appreciable amounts of NADPH, G6PD is upregulated by the increased ratio of [$NADP^+$]/[NADPH], resulting in facilitation of the G6P flux into the oxidative phase of the PPP [10].

The time course of ataxia onset in WE parallels a decrease in the activity of TK irrespective of that of PDHC and αKGDH, which has been considered the most sensitive measure of dietary thiamine deficiency [5, 11]. TK purified from cultured skin fibroblasts of patients with WKS was found to combine with its cofactor TPP with lower affinity than the enzyme from control fibroblasts; however, abnormalities for the PDHC and αKGDH were not observed in these subjects [4]. Moreover, differences of sensitivity in predisposition to WKS among subjects with TPP deficiency can be explained by biochemical variations in TK activity, which are ascribed to differences in assembly of the functional holoenzyme or differences in modification of the primary translation product [8]. The pathological lesions of KS are characterized by atrophy in the mammillary bodies and the medial dorsal thalamus [5, 6, 7]. Small hemorrhages in the mammillary bodies are observed in WE as preceding lesions of the mammillary atrophy in KS and are thought to occur due to the blood-brain barrier damage [12]. Demyelination, neurodegeneration, and blood-brain barrier damage have been identified as a sequence of histopathological changes in WKS [12]. TK is mainly localized on nearly all mature oligodendrocytes in human white matter and plays an important role in the process of lipogenesis when demands of NADPH are elevated during myelin formation [13]. Therefore, the demyelinating peculiarity found in WKS may be attributed to impairments of fatty acid biosynthesis and myelin formation due to reduced TK activity which predisposes the decrease in generation of NADPH due to failure in conversion of metabolic flow from R5P into the glycolysis intermediates. Following such primary event, accumulation of the local bleedings following the blood-brain barrier damage and consequent neurodegeneration would eventually trigger the discernible lesions of WKS, such as the mamillary bodies and other regions including the anterior region of the thalamus (accounting for amnesic symptoms [14]) and the medial dorsal thalamus.

This speculation provides a feasible explanation why thiamine deficiency causes WKS. However, emerging views are slightly inconsistent with the classical idea that NADPH derived from the oxidative phase of the PPP is important for the survival of brain cells. For example, individuals with G6PD deficiency, the most common human enzymopathy, experience haemolytic anaemia and often suffer from kernicterus attributable to neonatal jaundice [15]. These symptoms are reportedly due to a decreased generation of NAPDH caused by a lower G6PD activity. However, primary impairments of the central nervous system are uncommon [15]. Why G6PD deficiency does not typically cause brain damage in humans remains unknown; however, a lack of NADPH in cells other than erythrocytes may be compensated by other pathways. NADPH is formed by several enzymes other than the PPP, such as NADP-dependent malic enzyme (ME), $NADP^+$-dependent isocitrate dehydrogenase (ICDH), and nicotinamide nucleotide transhydrogenase (NNT) [16]. Compensation of NADPH is presumably due to additional enzymes not active in erythrocytes that are particularly susceptible to low G6PD levels [15]. Given that erythrocytes possess no mitochondria, fragility of erythrocytes against oxidative attacks may be ascribed to the absence of mitochondrial enzymes including mitochondrial malic enzyme (mME), ICDH and NNT. On the other hand, since brain has the mitochondria containing these enzymes, some type of compensatory mechanism for impairments of the PPP-associated NADPH generation may be involved in suppression of potential damages in the brain with G6PD deficiency.

Why the lack of NADPH in WKS patients is not compensated by the above-mentioned enzymes should be elucidated. Brain cells may rely on the activity of ME when the requirements for NADPH reducing equivalents must be met. ME catalyzes the reversible formation of malate from pyruvate and CO_2 depending on NADPH and magnesium ion or manganous ion (manganese (II) ion) but not manganic ion (manganese (III) ion):

malate + $NADP^+ \rightleftarrows$ pyruvate + CO_2 + NADPH + H^+.

Whereas ME has been considered to act in the carboxylating direction (to the left) in the liver and the heart, it reportedly acts as a decarboxylating enzyme (to the right) in the brain [16, 17]. However, to the best of our knowledge, whether oligodendrocytes express ME remains

unknown [18]. In addition, ICDH and NNT are apparently not associated with lipogenesis in oligodendrocytes. ICDH isozymes are localized either in the cytosol (*e.g.*, cytosolic ICDH; cICDH) or in the mitochondria (*e.g.*, mitochondrial ICDH, mICDH). Substantial activities of cICDH and mICDH are found in all types of brain cells, but ICDHs are likely involved in regeneration of cytosolic NADPH during peroxide disposal [19, 20]. NNT is a mitochondrial inner membrane protein functioning as a redox-driven proton pump, which catalyzes reduction of $NADP^+$ into NADPH coupled with conversion of NADH into NAD^+ [21]. This implies that generation of NADPH from NADH occurs in the mitochondria. However, a direct link between NAD^+/NADH and $NADP^+$/NADPH pools has not been reported in the cytosol [16]. A primary role of NNT is presumably the disposal of H_2O_2 through reduction of glutathione, although the physiological roles of NNT in the brain remain unclear.

Therefore, to the best of our knowledge, demyelination of oligodendrocytes found in WKS patients could be associated with the failure to compensate for the lack of NADPH due to thiamine deficiency. Since the PPP is highly active in oligodendrocytes where approximately 10% of glucose is metabolized *via* the PPP [18], it would be relevant to consider that generation of NADPH in the cells is thoroughly dependent on the oxidative phase of the PPP. However, why individuals with G6PD deficiency are unlikely to experience apparent impairments of oligodendrocytes remains unexplained. In fact, a functional defect in an enzyme involved in the PPP does not necessarily predispose impairments of the central nervous system. For example, the majority of individuals with a deficiency of transaldolase (TA), which catalyzes a reversible conversion of S7P and GAP into E4P and F6P, display normal mental and motor development [22, 23]. TA is not essential for generation of R5P, but supports generation of R5P from glycolysis intermediates GAP and F6P when more nucleotides and nucleic acids are needed [9]. These instances indicate a link between the PPP and glycolysis may be less important for neuronal development and function under normal G6PD activity. Instead, normal development and survival of the brain cells would necessitate formation of R5P through the non-oxidative phase of the PPP. Therefore, the reason why G6PD deficiency causes no impairments in the central nervous system is explicable by the possibility that production of R5P is not impaired in the brain cells with a lack of G6PD activity [24].

The R5P Demands of the Brain

In the non-oxidative phase, the reversible reactions allow ribulose 5-phosphate to be metabolized either to R5P *via* ribose 5-phosphate isomerase (R5P isomerase) or glycolysis intermediates, including F6P and GAP, *via* TK and TA [9]. The former reaction is necessary for nucleotide synthesis. ATP and R5P are converted into AMP and 5-phosphoribosyl-1-pyrophosphate (PRPP) by ribose-phosphate diphosphokinase (known as PRPP synthetase). PRPP reacts with purine derivatives (i.e., adenine, guanine, and hypoxanthine) to form purine nucleotides (*i.e.*, AMP, GMP, and IMP) by transferases (*i.e.*, adenine phosphoribosyltransferase: APRT, and hypoxanthine-guanine phosphoribosyltransferase: HGPRT) involved in the purine salvage pathway. The *de novo* synthesis of purine nucleotides also requires PRPP, but it does not function in the human brain. Indeed, in mature brain that almost lacks *ex novo* synthesis of purine and pyrimidine nucleotides, the salvage synthesis is crucially essential [25]. The transferred ribose is a basic component of numerous cellular intermediates, including ribonucleosides (*e.g.*, adenosine, guanosine, 5-methyluridine, uridine, and cytidine), ribonucleotides (*e.g.*, AMP, GMP, m5UMP, UMP, and CMP), cyclic nucleotides (*e.g.*, cAMP, and cGMP), ribonucleoside diphosphates (*e.g.*, ADP, GDP, m5UDP, UDP, and CDP), nucleoside triphosphates (*e.g.*, ATP, GTP, m5UTP, UTP, and CTP), coenzyme A, FAD, NAD^+, NADH, $NADP^+$, and NADPH. For instance, a 1,400 g human brain produces 7.7 mmol of ATP each minute [26], therefore, 5,600 g of ATP is consumed a day, which is 4 times the weight of the brain. The majority of ATP is not usually synthesized *de novo*, but it is resynthesized from ADP. The human brain contains approximately 1 g of ATP and thus the repeat of consumption and resynthesis of one molecule of ATP is estimated to occur 5,600 times a day. However, the frequency of ATP turnover in the brain appears to be much higher than in the body, which is estimated to be approximately 1,000–1,500 times a day [27]. Although the accurate amount of R5P necessary for *de novo* synthesis of ATP in the brain remains to be fully elucidated, we can infer *a priori* that high frequency of brain ATP turnover requires *de novo* synthesis of ATP more than the other organs, therefore suggesting greater demands of R5P in the brain. In addition, post-mitotic neurons do not proliferate, however, DNA repair would be essential to maintain integrity of the genome because the lifespan of neurons in the human brain is many decades [28]. Since the post-mitotic neurons would encounter a significant risk of oxidative DNA damages due to their high rate of oxidative metabolism [29], the increased flux of G6P into the PPP might be important for the promotion of the nucleotide synthesis by providing R5P, in addition to leading to increased production of the anti-oxidant cofactor NADPH [28]. Therefore, the role of PPP in meeting demands of the brain for R5P as a donor of numerous intermediates including ATP, $NAD(P)^+$, NAD(P)H, RNA and DNA might be more extensive than previously thought.

More interestingly, in individuals with deficiency of R5P isomerase, an enzyme that catalyzes a reversible conversion between ribulose 5-phosphate and R5P in the non-oxidative phase of the PPP, slow psychomotor development and serious mental retardation, perhaps attributable to slowly progressive leukoencephalopathy, have

been reported [30, 31]. The pathological findings have been thought due to the accumulation of the pentitols, such as ribitol and D-arabitol, as metabolic end products in the brain [30, 32]. Although polyols are particularly abundant in the central nervous system in normal individuals [33], extreme accumulation of polyols in the brain may be involved in the pathological characteristics of R5P isomerase deficiency. However, this hypothesis may not be valid because individuals with TA deficiency, who also present with elevated levels of ribitol, D-arabitol, and erythritol in plasma [22, 23], exhibit normal mental and motor development. Rather, this situation may support the hypothesis that generation of R5P *via* R5P isomerase is essential for the survival of any brain cell. Because formation of R5P from 6-phosphogluconate was reduced in the patient compared with normal individuals [30], a failure in meeting demands of the brain cells for R5P as a donor of ATP, $NAD(P)^+$, NAD(P)H, RNA and DNA may be associated with the patient's pathology. Based on comparison between subjects with G6PD deficiency and those with R5P isomerase deficiency, brain cells appear to prefer R5P to NADPH, suggesting the non-oxidative phase of the PPP is more imperative for the cells' survival than the oxidative phase.

Which phase of the PPP, the oxidative or the non-oxidative, would be more important for a cell with the increased demands for nucleotides? For example, TK is overexpressed in cancer cells and probably foremost for the synthesis of nucleotides necessary to sustain their proliferation [34]. Three different genes of TK have been identified in human genome: one TK gene (TKT) and two transketolase-like genes (TKTL1 and TKTL2) [35]. Increased expression of TKTL1, which strongly enhances the generation of R5P and E4P from GAP and F6P, is found in colon cancer, whereas TKT and TKTL2 transcripts are not upregulated [34]. Enhanced TKTL1 highly correlates with both the speed of tumour growth and invasiveness, as well as poor patient outcome [34]. In nucleotide synthesis processes of cancer cells, the necessity for R5P *via* the non-oxidative PPP appears to exceed NADPH *via* the oxidative PPP; 70% of ribose isolated from tumour cell RNA is synthesized through the TPP-dependent TK reaction, whereas ribose derived from the oxidative phase of the PPP only accounts for less than 30% of total RNA [36]. *In vitro* and *in vivo* administration of dehydroepiandrosterone sulfate (DHEA-S), a non-competitive inhibitor of G6PD, is less potent in inhibiting tumour cell proliferation than treatment with the TK inhibitor oxythiamine, indicating R5P is primarily synthesized through the TK pathway in tumour cells and oxythiamine inhibits the synthesis more effectively than DHEA-S [37]. Although combined intervention of both oxythiamine and DHEA-S might have potential as a new strategy to deter cancer development by completely inhibiting ribose synthesis [38], to the best of our knowledge, whether adverse effects to the central nervous system occur when both drugs are administered to humans has not been reported to date.

Conclusion

By analogy from the above-mentioned example for cancer cells, it is inferred that oligodendrocytes with the increase in lipogenesis prioritize generation of R5P more than that of reducing equivalents of NADPH. Therefore, keeping the high rate of turnover of NADPH required for myelination might necessitate *de novo* synthesis of NADPH from R5P *via* the non-oxidative phase more than reduction of $NADP^+$ to NADPH through the oxidative phase. In conclusion, demands for R5P in brain cells are greater than previously thought, and the decreased TK activity might cause a failure in the conversion of ribulose 5-phosphate into the glycolysis intermediates when a need for NADPH is greater than that for R5P. However, a predisposition to insufficient supply of NADPH may depend on the amount of R5P required in a cell. Therefore, specific lesions such as the demyelination of oligodendrocytes found in WKS might be determined not only by decreased levels of NADPH reducing equivalents, but also by an increase in latent demands of R5P in oligodendrocytes. Thorough understanding awaits further investigations and the complete elucidation of TK's role in a reversible link between glycolysis and the PPP would increase the knowledge of the WKS pathology in terms of substantial cellular demands for R5P and NADPH.

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