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Review Article

How Does Thiamine Deficiency Induce the Wernicke-Korsakoff Syndrome?

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Review

For all brain cells, glucose is a major source of common energy currency; i.e., adenosine triphosphate (ATP). A Primary Mechanism to Produce 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 dexterously regulated in response to ATP demands by various enzyme reactions [1]. Some of the reactions require vitamins as an essential cofactor in order to exert their catalytic actions. Thiamine (vitamin B1) is converted to Thiamine Pyrophosphate (TPP) of its active form and subsequently serves as a coenzyme of several enzymes related to the glucose metabolism, such as transketolase (TK), Pyruvate Dehydrogenase Complex (PDHC) and α-ketoglutarate dehydrogenase (αKGDH) [2,3]. Insufficient intake of TPP can reduce the activity of these enzymes, consequently leading to energy compromise along with lactic acidosis, which can cause profound impairment on the biological functions [4]. As for the brain, Wernicke Encephalopathy (WE) is well known to be produced by thiamine deficiency, which is characterized by clinical signs such as delirium, confusion, significant spatial and temporal disorientation, memory impairment, ataxia, nystagmus and ophthalmoplegia [5]. Although WE is treatable with adequate replenishment of thiamine, prolonged insufficiency of thiamine could bring about the significant sequela, i.e., Korsakoff's Syndrome (KS) which is featured by fixed impairment of memory functions, including lack of insight, anterograde amnesia, retrograde amnesia, and confabulation [6,7]. Whether KS can develop without WE remain controversial, I previously reported a case who had developed KS along with pellagra due to chronic undernourishment with having neither apparent histories of chronic alcoholics nor some episode suggestive of WE [8]. Uncertainty as to whether or not WE always precedes KS might be explained by the fact that the clinical diagnosis of WE is very difficult and therefore often missed [9], but the case taught us that abnormalities of the brain energy metabolism resulted from malnutrition could bring about calamitous damages to the brain's executive functions.

To clarify the pathological changes in the Wernicke-Korsakoff Syndrome (WKS), many investigators have focused on TK, PDHC, and αKGDK. Among them, TK has been regarded as most relevant pathogenesis of WKS [10]. A decrease in the TK activity parallels the time course of ataxia onset and has been considered the most sensitive measure of dietary thiamine deficiency [11,12]. TK purified from cultured skin fibroblasts of persons with WKS has been found to be bound its cofactor TPP with lower affinity than the enzyme from control fibroblasts; however, neither abnormalities for the PDHC nor αKGDH were observed in these people [5], suggesting involvement of TK in the pathogenesis of WKS. Moreover, differences of sensitivity in predisposition to WKS among people with TPP deficiency can be explained by biochemical variations of TK activity, which are ascribed to differences in assembly of the functional holoenzyme or differences in modification of the primary translation product [10]. The pathological lesions of KS are characterized by atrophy in the mammillary bodies and the medial dorsal thalamus [8]. Small hemorrhages in the mammillary bodies are observed in WE as preceding lesions of the mammillary atrophy in KS and are supposed to occur due to the blood-brain barrier damage. Demyelination, neurodegeneration, and blood-brain barrier damage have been identified as a sequence of histopathological changes of WKS [13]. TK is mostly localized on nearly all mature oligodendrocytes in human white matter [14]. TK catalyzes two (the first and last) of the three steps of 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 [15]. The enzyme plays an important role in creating a reversible link between glycolysis and the PPP. Biosynthetic reactions including lipogenesis and myelin formation require appreciable amount of nicotinamide adenine dinucleotide phosphate (NADPH) [16]. Since all of the 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 NAPDH is greater than that for R5P, ribulose 5-phosphate is converted into the glycolysis intermediates, GAP and F6P, which are used to generate G6P. Whether the resultant G6P enters the PPP or not is dependent on activity of glucose 6-phosphate dehydrogenase (G6PD) that is the regulatory enzyme of the PPP. Since G6PD is stimulated by its substrate G6P and is mainly upregulated by the increased ratio of [$NADP^+$]/[NADPH], elevated demands of NADPH during myelin formation result in facilitation of the G6P flux into the oxidative phase of the PPP. Therefore, the demyelinating peculiarity found in WKS might have been attributed to impairments of fatty acid biosynthesis and myelin formation due to reduced activity of TK [14]. Following such primary event, accumulation of local abnormalities including the blood-brain barrier damage would eventually trigger the local bleedings, as well as neurodegeneration, in the discernible lesions of WKS, such as the mammillary bodies and other regions including the anterior region of the thalamus (accounting for amnesic symptoms [17] and the medial dorsal thalamus.

This speculation provides us with a feasible reason why thiamine deficiency causes WKS. However, there are emerging views to be somewhat inconsistent with the classical idea that NADPH derived from the oxidative phase of the PPP is important for neuronal survival. For instance, in people with the most common human enzymopathy 'G6PD deficiency', who have a chief problem of hemolytic anemia and often suffer from kernicterus attributable to neonatal jaundice, primary impairments of the central nervous system are distinctly uncommon [18]. The facts that G6PD deficiency causes none of sever neurological symptoms in humans arouse us to conceive that a lack of NADPH can be compensated by other pathways to supply it. Indeed, there are several pathways to generate NADPH other than the PPP, which include NADP-dependent malic enzyme (ME), $NADP^+$-dependent is citrate dehydrogenase (ICDH), and nicotinamide nucleotide transhydrogenase (NNT) [19]. Perhaps, compensation of NADPH is presumed due to additional enzymes not active in erythrocytes that are particularly susceptible to low levels of G6PD [18]. 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.

Besides activity of the PPP, the brain cells may rely on the activity of ME when they must modify requirements for NADPH reducing equivalents. ME exists in two isoforms, mME and cytosolic malic enzyme (cME), of which the cME is strictly dependent on $NADP^+$, albeit mME can use either NAD^+ or $NADP^+$ [16]. The distribution of ME isozymes differs between neurons and astrocytes. mME highly exists in neurons, whereas cME is not detected in neurons [20]. Astrocytes have both isozymes, but cME accounts for as much as 95% of total ME activity in the cells [20]. mME in the neurons plays important roles in at least three relevant processes including; (1) reduction of the small, but critical amount of intramitochondrial glutathione (GSH) with NADPH, which elicits antioxidative effects against the mitochondria [21], (2) metabolizing a variety of xenobiotic through mitochondrial cytochrome P450 systems with NADPH [22], and (3) recycling of pyruvate [23]. The recycled pyruvate is converted to Acetyl-CoA and then to citrate, but it cannot be converted to oxaloacetate (OAA) due to the absence of pyruvate carboxylase (PCase) in the mitochondria of neurons. The neuronal mitochondria are almost distributed in both the cell body and the synaptic terminals. In the cerebral cortical neurons, the activity of mME is even higher in the synaptic terminals than in the cell bodies [20], which may be of great advantage to prevent the cells from oxidative damage attributable to hydrogen peroxide (H_2O_2). In the synaptic terminal of monoaminergic neurons, monoamine oxidase (MAO) exists on the outer membrane of the mitochondria and catalyzes the oxidative deamination of monoamines (e.g., norepinephrine, epinephrine, serotonin, and dopamine are catalyzed by MAO-A, and dopamine is oxidized also by MAO-B). Since MAO generates H_2O_2 that has a very strong oxidizing capacity, mitochondrial glutathione reductase/glutathione peroxidase is necessary to eliminate H_2O_2 derived from MAO activity [24]. To scavenge radical species, monoaminergic neurons may depend to a large extent on the higher activity of mME that can provide appreciable amounts of NADPH enough to reduce glutathione. Interestingly, a recent report provided evidence showing that genetic variation in or near the mME gene is associated with both psychotic and manic disorders, including schizophrenia and bipolar disorder [25]. Given pathogenetic involvement of monoaminergic neurons in these psychotic disorders, this intriguing result allows us to envision a scenario that some dysfunction of mME introduces impairment of monoamine metabolism to neurons through insufficient elimination of H_2O_2 related to a heightened activity of mitochondrial MAO.

On the other hand, cME is identified in astrocytes exclusively. Astrocytes have both cME and mME, and cME is highly enriched in astrocytes [16,20,26,27]. A plentiful cME participates in generation of NADPH in astrocytes under unstressed conditions. cME contributes to generation of pyruvate from malate in the cytosol, and the resultant cytosolic pyruvate reenters the mitochondria and then can be converted either to OAA by PCase or to acetyl-CoA by PDH. If not reenter the mitochondria, pyruvate would be oxidized to lactate by LDH or be converted to alanine by ALT in the cytosol. The cytosolic NADPH contributes to anabolic pathways; including lipid synthesis, cholesterol synthesis, and fatty acid chain elongation, as well as reduction of GSSG to GSH. In addition, NADPH is required as a cofactor of NOS when NO is generated [28]. However, since cME cannot supply sufficient NADPH to keep the cellular redox potential low during oxidative stress [29], astrocytes have to rely on the PPP as NADPH source on the stress

condition. Indeed, increased ratio of the [$NADP^+$]/[NADPH] leads to allosteric activation of G6PD under the oxidative stress, which results in increased generation of NADPH.

By the way, because astrocytes have PCase specifically in the mitochondria, coexistence of two enzymes, PCase and mME, in the same compartment appears to be at risk for developing a futile cycle. Therefore, even if pyruvate is carboxylated to OAA through PCase that uses ATP, OAA is reduced to malate with a cost of NADH and then malate is decarboxylated to pyruvate through mME in which either NADPH or NADH is generated. This cycle seems to be futile, because one ATP is only consumed without producing any substances in each one turn of this cycle [19]. This cycle, however, may contribute to generation of less than one NADPH in the mitochondria at the expense of both one ATP and one NADH. Since such a vain cycle seems unlikely to operate except for a special situation in which NADPH is absolutely required in the mitochondria, it is supposed to be one of the reasons why mME exists little in astrocytes. The futile cycling between PCase and mME may participate in avoiding the over-production of ATP. Or this futile cycle may be involved in some formation of the bistability or the switching between the two states of the intramitochondrial NADH levels. Anyway, to elucidate how astrocytes protect their mitochondria with almost lack of mME from the attack of ROS remains as a very interesting problem.

Brain cells can reduce $NADP^+$ into NADPH by using several enzymes other than the enzymes related to the oxidative phase of PPP (i.e., G6PD and 6-phosphogluconate dehydrogenase) and the ME pathway (i.e., mME and cME). For example, $NADP^+$-dependent isocitrate dehydrogenase (ICDH), and nicotinamide nucleotide transhydrogenase (NNT) contribute to regeneration of NADPH [19]. ICDH isozymes are localized either in the cytosol (i.e, cytosolic ICDH; cICDH) or in the mitochondria (i.e., mitochondrial ICDH, mICDH). Substantial activities of cICDH and mICDH are found in all kinds of brain cells, and ICDHs are likely involved in regeneration of cytosolic NADPH during peroxide disposal [30,31]. On the other hand, NNT is a mitochondrial inner membrane protein functioning as a redox-driven proton pump, which catalyzes reduction of $NADP^+$ into NADPH in coupling with conversion of NADH into NAD^+ [32]. This implies that generation of NADPH from NADH occurs in mitochondria. However, a direct link between NAD^+/NADH and $NADP^+$/NADPH pools has not been reported for the cytosol [19]. A primary role of NNT has been thought to be disposal of H_2O_2 through reduction of glutathione, although little is still known about the physiological roles of NNT in the brain. NTT as well as mME and mICDH are considered to be associated with elimination of H_2O_2 in the mitochondria.

Intriguingly, in a person with deficiency of R5P isomerase that is an enzyme to catalyze 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 described [33,34]. The pathological findings were considered to be attributed to accumulation of pentoses and pentose phosphates, in turn leading to accumulation of the pentitols ribitol and D-arabitol as metabolic end products in the brain [33,34]. Although polyols are particularly abundant in the central nervous system in normal individuals [35], extreme accumulation of polyols in the brain may be ascribed to the pathology of the patient with R5P isomerase deficiency. However, this case may also support a feasible idea that generation of R5P via R5P isomerase is essential for survival of any of the cells constituting the brain, because formation of R5P from 6-phosphogluconate was reduced in the patient compared with normal individuals [34]. This result is very interesting in the way that R5P isomerase deficiency causes impairment of the R5P formation whereas R5P is supposed to be generated by interconversions of the non-oxidative intermediates derived from the glycolytic intermediates.

More interestingly, the majority of people with deficiency of transaldolase that catalyzes a reversible conversion of S7P and GAP into E4P and F6P express normal mental and motor development [36]. Since part of transaldolase is to support generation of R5P from glycolysis intermediates GAP and F6P when more nucleotides and nucleic acids are needed, these cases suggest that a link between the PPP and glycolysis may be less important for neuronal development under the condition of the normal G6PD activity. For speculations of the above-mentioned reports, it is conceivable that normal development and survival of the brain cells may necessitate formation of R5P through the non-oxidative phase of the PPP. The reason why G6PD deficiency causes no impairments in the central nervous system is explicable by the possibility that no lack of R5P occurs. Rather, roles of the PPP in generation of R5P as a donor of a myriad of intermediates including ATP, $NAD(P)^+$, NAD(P)H, RNA, and DNA may be larger than previously thought. However, post-mitotic neurons do not proliferate. Why do they need R5P as a precursor of DNA? Given many-decades lifespan of post-mitotic neurons in the human brain, DNA repair is highly essential to maintain integrity of the genome [37]. Since the post-mitotic neurons would face a grave risk of oxidative DNA damages due to their high rate of oxidative metabolism [38], the increased flux of G6P into the PPP might be relevant to promotion of the nucleotides synthesis by providing R5P, besides leading to increased production of the anti-oxidant cofactor NADPH [37]. Further investigations are awaited, because very little is known about the relation between neuroprotection and roles of the PPP in R5P generation. The complete elucidation of roles of TK in a link between glycolysis and the PPP, as well as in redox regulation between NAD^+/NADH and $NADP^+$/NADPH, would deepen our understanding of the pathology of WKS due to thiamine deficiency.

References

1. Stryer L (2000) Integration of metabolism. Biochemistry. New York: W. H. Freeman and Company 627-645
2. Lohmann K, Schuster P (1937) Untersuchungen über die Cocarboxylase. Biochem Z 294: 188-214.
3. McCandless DW (2010) Thiamine deficiency and associated clinical disorders. New York: Humana Press.
4. Butterworth RF (1989) Effects of thiamine deficiency on brain metabolism: implications for the pathogenesis of the Wernicke-Korsakoff syndrome. Alcohol and alcoholism 24: 271-279.
5. Blass JP, Gibson GE (1977) Abnormality of a thiamine-requiring enzyme in patients with Wernicke-Korsakoff syndrome. N Engl J Med 297: 1367-1370.
6. Nyssen R (1960) [Study of "Amnesia Of Fixation" in Korsakoff's disease by non-repeated acquisition tests]. Acta neurologica et psychiatrica Belgica 60: 783-793.
7. Zubaran C, Fernandes JG, Rodnight R (1997) Wernicke-Korsakoff syndrome. Postgraduate medical journal 73: 27-31.
8. Shintani F, Izumi M (2010) Black legs. BMJ 341: c3511.
9. Arts NJ, Walvoort SJ, Kessels RP (2017) Korsakoff's syndrome: a critical review. Neuropsychiatr Dis Treat 13: 2875-2890.
10. Martin PR, McCool BA, Singleton CK (1995) Molecular genetics of transketolase in the pathogenesis of the Wernicke-Korsakoff syndrome. Metab Brain Dis 10: 45-55.
11. Butterworth RF (1995) Pathophysiology of alcoholic brain damage: synergistic effects of ethanol, thiamine deficiency and alcoholic liver disease. Metab Brain Dis 10: 1-8.
12. Victor M, Adams RD, Collins GH (1989) The Wernicke-Korsakoff syndrome and related neurologic disorders due to alcoholism and malnutrition. 2nd ed. J Neurol Neurosurg Psychiatry 52: 1217-1218.
13. Hazell AS, Todd KG, Butterworth RF (1998) Mechanisms of neuronal cell death in Wernicke's encephalopathy. Metab Brain Dis 13: 97-122.
14. Lovato L, Cianti R, Gini B, Marconi S, Bianchi L, et al. (2008) Transketolase and 2',3'-cyclic-nucleotide 3'-phosphodiesterase type I isoforms are specifically recognized by IgG autoantibodies in multiple sclerosis patients. Molecular & cellular proteomics 7: 2337-2349.
15. Harvey RA, Ferrier DR (2011) Lippincott's illustrated reviews: Biochemistry. 5th ed. Philadelphia: Wolters Kluwer Health
16. Hertz L, Dienel GA (2002) Energy metabolism in the brain. Int Rev Neurobiol 51:1-102.
17. Konishi K (2009) The cognitive profile of elderly Korsakoff's syndrome patients.
18. Cappellini MD, Fiorelli G (2008) Glucose-6-phosphate dehydrogenase deficiency. Lancet 371: 64-74.
19. Gibson GE, Dienel GA (2007) Handbook of Neurochemistry and Molecular Neurobiology: Brain Energetics. Integration of Molecular and Cellular Processes. New York.
20. McKenna MC, Stevenson JH, Huang X, Tildon JT, Zielke CL, et al. (2000) Mitochondrial malic enzyme activity is much higher in mitochondria from cortical synaptic terminals compared with mitochondria from primary cultures of cortical neurons or cerebellar granule cells. Neurochem Int 36: 451-459.
21. Vogel R, Jennemann G, Seitz J, Wiesinger H, Hamprecht B (1998) Mitochondrial malic enzyme: purification from bovine brain, generation of an antiserum, and immunocytochemical localization in neurons of rat brain. J Neurochem 71: 844-852.
22. Ravindranath V, Bhamre S, Bhagwat SV, Anandatheerthavarada HK, Shankar SK, et al. (1995) Xenobiotic metabolism in brain. Toxicol Lett 82-83: 633-638.
23. Cruz F, Scott S, Barroso I, Santisteban P, Cerdán S. Ontogeny and cellular localization of the pyruvate recycling system in rat brain. J Neurochem 70 : 2613-2619.
24. Zoccarato F, Toscano P, Alexandre A (2005) Dopamine-derived dopaminochrome promotes H(2)O(2) release at mitochondrial complex I: stimulation by rotenone, control by Ca(2+), and relevance to Parkinson disease. J Biol Chem 280: 15587-15594.
25. Lee BD, Walss-Bass C, Dassori A, Montero PA, Thompson PM, et al. (2007) Malic enzyme 2 and susceptibility to psychosis and mania. Psychiatry Res 150: 1-11.
26. McKenna MC (2007) The glutamate-glutamine cycle is not stoichiometric: fates of glutamate in brain. J Neurosci Res 85: 3347-3358.
27. Kurz GM, Wiesinger H, Hamprecht B (1993) Purification of cytosolic malic enzyme from bovine brain, generation of monoclonal antibodies, and immunocytochemical localization of the enzyme in glial cells of neural primary cultures. J Neurochem 60: 1467-1474.
28. Ma L, Morita I, Murota S (1994) Presence of constitutive type nitric oxide synthase in cultured astrocytes isolated from rat cerebra. Neurosci Lett 174: 123-126.
29. Filosa S, Fico A, Paglialunga F, Paglialunga F, Balestrieri M, et al. Failure to increase glucose consumption through the pentose-phosphate pathway results in the death of glucose-6-phosphate dehydrogenase gene-deleted mouse embryonic stem cells subjected to oxidative stress. Biochem J 370: 935-943.
30. Harman AW, Nieminen AL, Lemasters JJ, Herman B (1990) Cytosolic free magnesium, ATP and blebbing during chemical hypoxia in cultured rat hepatocytes. Biochem Biophys Res Commun 170: 477-483.
31. Minich T, Yokota S, Dringen R (2003) Cytosolic and mitochondrial isoforms of NADP+-dependent isocitrate dehydrogenases are expressed in cultured rat neurons, astrocytes, oligodendrocytes and microglial cells. J Neurochem 86: 605-614.
32. Freeman H, Shimomura K, Cox RD, Ashcroft FM (2006) Nicotinamide nucleotide transhydrogenase: a link between insulin secretion, glucose metabolism and oxidative stress. Biochem Soc Trans 34: 806-810.
33. van der Knaap MS, Wevers RA, Struys EA, Verhoeven NM, Pouwels PJ, et al. (1999) Leukoencephalopathy associated with a disturbance in the metabolism of polyols. Ann Neurol 46: 925-928.
34. Huck JH, Verhoeven NM, Struys EA, Salomons GS, Jakobs C, et al. (2004) Ribose-5-phosphate isomerase deficiency: new inborn error in the pentose phosphate pathway associated with a slowly progressive leukoencephalopathy. Am J Hum Genet 74: 745-751.
35. Kusmierz J, DeGeorge JJ, Sweeney D, May C, Rapoport SI (1989)

Quantitative analysis of polyols in human plasma and cerebrospinal fluid. J Chromatogr 497: 39-48.

36. Wamelink MM, Struys EA, Jakobs C (2008) The biochemistry, metabolism and inherited defects of the pentose phosphate pathway: a review. J Inherit Metab Dis 31: 703-717.

37. Merlo D, Di Stasi AM, Bonini P, Mollinari C, Cardinale A, et al. (2005) DNA repair in post-mitotic neurons: a gene-trapping strategy. Cell Death Differ 12: 307-309.

38. Fishel ML, Vasko MR, Kelley MR (2007) DNA repair in neurons: so if they don't divide what's to repair? Mutat Res 614: 24-36.