Pathophysiology of Cerebellar Dysfunction in the Wernicke-Korsakoff Syndrome

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ABSTRACT: Cerebellar ataxia is a common presenting sign in the Wernicke-Korsakoff syndrome (WKS). Recovery from ataxia following thiamine treatment is rarely complete, suggesting the existence of both a reversible ("biochemical") lesion as well as irreversible, neuropathological damage. Cerebellar pathology in WKS includes severe loss of Purkinje cells in superior cerebellar vermis as well as neuronal loss from the granular layer. In addition, damage to inferior olivary nucleus could result in loss of climbing fibre input to cerebellum in this condition. Experiments using an animal model of WKS, the pyrithiamine-treated rat, reveal selective reversible decreases of α-ketoglutarate dehydrogenase (αKGDH) in cerebellum. Decreased enzyme activities are associated with decreased cerebellar content of GABA and aspartate. Thiamine reversal of neurological symptoms results in normalization of cerebellar enzyme activities and GABA content suggesting that reduced activities of αKGDH constitute "the biochemical lesion" in these animals. Possible mechanisms implicated in neuronal cell death in cerebellum include impaired cellular energy metabolism, focal lactic acidosis and excitotoxic damage resulting from excess glutamate release mediated by N-methyl-D-aspartate (NMDA) receptors. Similar mechanisms could be involved in the reversible and irreversible neurological symptoms of WKS in humans.

RÉSUMÉ: Pathophysiologie de la dysfonction cérébelleuse dans le syndrome de Wernicke-Korsakoff. L'ataxie cérébelleuse est un mode de présentation fréquent du syndrome de Wernicke-Korsakoff (SWK). La récupération est rarement complète suite au traitement par la thiamine, suggérant la co-existence d'une lésion réversible ("biochimique") et d'une lésion irréversible, un dommage neuropathologique. La pathologie cérébelleuse dans le SWK comprend une perte sévère de cellules de Purkinje dans le vermis cérébelleux supérieur ainsi qu'une perte neuronale dans la couche granuleuse de l'écorce cérébelleuse. Dans cette affection, l'atteinte de l'olive inférieure peut amener une perte de l'influx provenant des fibres grimpantes vers le cervelet. Des études effectuées sur un modèle animal de SWK, le rat traité à la pyrithiamine, révèlent une diminution réversible sélective de l'∝-kétoglutarate déshydrogénase (∝KGDH) dans le cervelet. Des activités enzymatiques diminuées sont associées à une diminution du GABA et de l'aspartate dans le cervelet. Le soulagement des symptômes neurologiques par la thiamine amène une normalisation des activités enzymatiques cérébelleuses et du contenu en GABA, suggérant qu'une activité de l'∝KGDH diminuée constitue la "lésion biochimique" chez ces animaux. Nous mentionnons l'atteinte du métabolisme énergétique cellulaire, une acidose lactique focale et un dommage excitotoxique résultant d'une libération excessive de glutamate par l'intermédiaire des récepteurs du N-méthyl-D-aspartate comme étant des mécanismes qui sont possiblement impliqués dans la mort des neurones cérébelleux. Des mécanismes semblables pourraient être impliqués dans la pathogenèse des symptômes neurologiques réversibles et irréversibles du SWK chez l'humain.

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The Wernicke-Korsakoff syndrome (WKS) is a neuropsychiatric disorder characterized by ophthalmoplegia, ataxia and global confusional state. Although frequently associated with chronic alcoholism, WKS is also encountered in cases of gastrointestinal carcinoma, AIDS, hyperemesis gravidarum and other conditions of grossly impaired nutritional status.[1]

Ataxia is a common presenting sign in WKS.[2] In initial phases of the illness, patients demonstrate loss of equilibrium of such severity that standing or walking without support may be impossible. Patients assume a stance with feet wide apart and trunk inclined forward as a slow, shuffling, short-stepped gait. In contrast to the severe disorder of locomotion, incoordination of movement is relatively infrequent.[2]

There is an abundant body of evidence to suggest that WKS results from thiamine deficiency. Chronic alcoholism results in thiamine deficiency due to inadequate dietary intake of the vitamin, impaired absorption from the gastrointestinal tract and depletion of liver and brain stores.[1] Brain cells require a continuous supply of thiamine. Saturable thiamine uptake by the brain occurs at a maximal rate of 0.3 μg/h/g brain tissue, a rate that is similar to that calculated for brain thiamine turnover, suggesting that thiamine transport may be just in excess of that required

with little spare capacity of the system. The highest thiamine turnover rates occur in cerebellum (0.551 µg/g/h compared to 0.159 µg/g/h for cerebral cortex).[1]

RECOVERY FROM ATAXIA FOLLOWING THIAMINE TREATMENT OF PATIENTS WITH WERNICKE'S ENCEPHALOPATHY

In the comprehensive study by Victor et al.,[2] 107 WKS patients with ataxia of stance or gait were studied both prior to and following thiamine treatment. Complete recovery from ataxia occured in 41 patients (38 per cent); in most cases, improvement began within 2 - 6 days after the start of thiamine treatment. The time required for complete recovery in these patients varied from 1 - 8 months. 37 patients (35 per cent) showed wide-based gait ataxia in all cases. Improvements again started within one week and maximal recovery was noted after 2 - 7 months. In a further 29 patients (27 per cent), no significant improvement from ataxia was noted following thiamine treatment for periods of more than 2 months.

Cerebellar Pathology in the Wernicke-Korsakoff Syndrome

Degeneration of the cerebellar cortex was described by Victor et al.[2] in 15 of 27 patients. The most striking change was a loss of Purkinje cells limited to the folia of the superior cerebellar vermis accompanied by an increase of Bergmann glia. In some cases there was also a partial loss of neurons from the granular layer, thinning of the molecular layer and concomitant astrocytic proliferation. It is generally presumed that the chronic ataxia of stance and gait results from lesions of the superior cerebellar vermis.[2]

Evidence strongly suggests that the cerebellar lesions encountered in Wernicke's encephalopathy and those of "alcoholic cerebellar degeneration" represent the same disease process. In one study of alcoholic cerebellar degeneration, Wernicke-type lesions were found at postmortem examination in 4 of 11 cases; in 3 of which, changes were restricted to the superior vermis.[2] In 7 cases of alcoholic cerebellar degeneration in a subsequent report, 6 were found to have associated Wernicke's encephalopathy.[3] More recently, a quantitative histological study of cerebellar vermis in 10 male alcoholics and 8 age-matched controls revealed a Purkinje cell loss of 21% in the alcoholic group.[4] Histological measurements of the area of the molecular and granular layers of the cerebellar vermis showed that the molecular layer varied in the degree of shrinkage between lobes (from 11 - 39%) while the granular layer showed a consistent 9 - 10% shrinkage. Brains from alcoholic patients with WKS had particularly low Purkinje cell counts and a large pericerebral space.[4]

Table 1. Cerebellar Pathology in Alcoholics With or Without WKS

	Cerebellar Wt. (g)	Purkinje Cell Density in Cerebellar Vermis (Number/mm)
normals (16)	181 ± 4	5.81 ± 0.29
alcoholics without WKS (12)	176 ± 5	5.65 ± 0.45
alcoholics with WKS (6)	154 ± 9 *	4.17 ± 0.16 *

* $p < 0.05$ compared to normals and alcoholics without WKS (data from Phillips et al. 1990, reference 5)

Experimental Animal Model of WKS: the Pyrithiamine Treated Rat

Pyrithiamine is a central thiamine antagonist. Daily treatment of rats with pyrithiamine results, within 2 weeks, in neurological symptoms and, ultimately, neuropathologic damage of a similar nature and distribution to that encountered in WKS in humans.[6,7] Thus, neuropathologic lesions of mammillary bodies, thalamus, lateral vestibular nucleus, inferior olivary nucleus and cerebellum are observed in the brains of symptomatic pyrithiamine-treated rats.[6]

Daily administration of pyrithiamine to rats results in diminished central stores of thiamine and thiamine pyrophosphate (TPP), the enzyme cofactor form of the vitamin.[8]

Cerebral Thiamine-Dependent Enzymes in WKS

Three important enzyme systems involved in brain glucose utilization are TPP-dependent, namely the pyruvate dehydrogenase complex (PDHC), α-ketoglutarate dehydrogenase (αKGDH) and transketolase (TK). The positions of these enzyme systems in relation to glucose metabolism are shown schematically in Figure 1.

Pyrithiamine-induced thiamine deficiency results in selective decreases of αKGDH in several brain structures including cerebellum[1,9] (Figure 2). Since αKGDH activities are close to the calculated flux of 3-carbon units derived from glucose in vivo, it has been suggested that αKGDH is rate limiting for brain glucose (and pyruvate) metabolism.[1] Decreased αKGDH in cerebellum of symptomatic pyrithiamine-treated rats is associated with increased alanine[1] and lactate,[10] consistent with decreased entry of pyruvate into the tricarboxylic acid cycle (see Figure 2).

Thiamine administration to symptomatic pyrithiamine-treated rats results in complete reversal of neurological symptoms (ataxia, loss of righting reflex). Cerebellar concentrations of alanine, GABA and αKGDH activities are concomitantly returned to normal (Figure 2). These findings suggest that the reversible decreases of αKGDH and decreased GABA synthesis most likely constitute "the biochemical lesion" in thiamine-deficiency encephalopathy. Extrapolation of these findings to WKS in humans suggests that thiamine reversal of ataxia is a consequence of normalization of defective αKGDH activities and GABA synthesis in cerebellum.

On the other hand, thiamine reversal of symptomatic pyrithiamine-treated rats does not result in complete reversal of aspartate deficits in the cerebellum of affected animals (Figure 2 and reference [1]). One possible explanation for this loss of aspartate could involve the start of a loss of climbing fibre input to the cerebellum in these animals, resulting from lesions to inferior olivary nucleus.[6]

Pathogenesis of Neuronal Death in WKS

Several mechanisms have been proposed to explain the selective loss of neurons in thiamine deficiency. Such mechanisms are: 1) impaired cellular energy metabolism; 2) focal accumulation of lactate and ensuing acidosis, and 3) excitotoxic damage due to glutamate release, mediated by the N-methyl-D-aspartate (NMDA) receptor.

αKGDH, being a rate-limiting tricarboxylic acid cycle enzyme, is intimately involved in mitochondrial energy metabolism. Thus, reductions of αKGDH, if sufficiently severe and prolonged, would be expected to result in decreased ATP
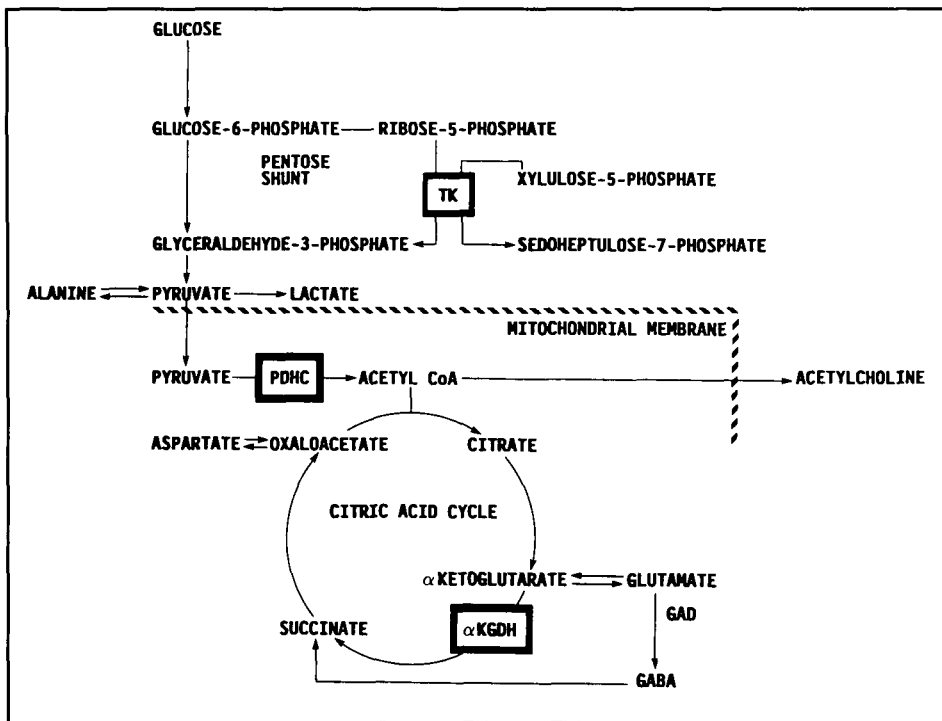
Figure 1 — Thiamine-dependent enzymes in relation to glucose metabolism and amino acid synthesis. PDHC: pyruvate dehydrogenase complex; αKGDH; α-ketoglutarate dehydrogenase; TK: trans-ketolase.

synthesis and ensuing compromise of cellular energy metabolism. Measurement of high energy phosphates in the brains of symptomatic pyrithiamine-treated rats revealed decreases of ATP and phosphocreatine in brainstem of affected

animals (Aikawa et al. 1984). Cerebellar high energy phosphates, on the other hand, were unchanged in these animals.

Increased brain lactate has consistently been observed in the brains of animals with thiamine deficiency[12,13] and it has been suggested that focal accumulation of lactate and the consequent pH changes could be responsible for neuronal loss in this condition.[10] In support of this possibility, a recent autoradiographic study using ^{14}C-dimethyloxazolinedione as pH marker, acidosis was observed in several brain regions including cerebellar cortex of symptomatic thiamine-deficient rats.[14] Furthermore, treatment of thiamine-deficient animals with the Ca^{2+} channel blocker nimodipine resulted in prevention of neurological symptoms and of acidosis in several brain structures of these animals, including cerebellum. It was suggested that pH changes were related to an improved ability of the brain to reduce its proton load in the presence of nimodipine.[14]

Finally, there is evidence to suggest that neuronal cell death in thiamine deficiency may be the result of N-methyl-D-aspartate (NMDA) receptor-mediated excitotoxic damage. The nature of the tissue damage in thiamine deficiency resembles that observed following anoxic/ischemic insults suggesting the involvement of excitatory amino acids. In support of this contention, treatment of animals with the NMDA receptor antagonist MK-801 led to a marked reduction of lesions in medial geniculate and mammillary bodies in pyrithiamine-treated animals.[15] Protective effects of NMDA receptor antagonists on
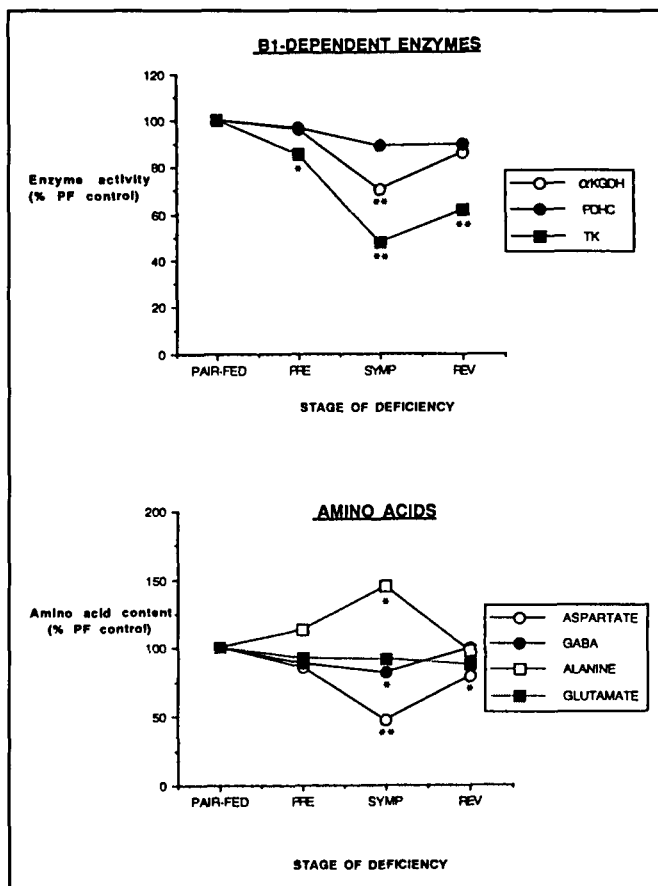
Figure 2 — Effects of pyrithiamine-induced thiamine deficiency and subsequent thiamine treatment on activities of thiamine-dependent enzymes and amino acids in cerebellum. Abbreviations for enzymes as in legend to Figure 1. PF: pair fed controls; PRE: presymptomatic stage; SYMP: symptomatic stage; REV: thiamine-reversed. Values significantly different from PF control values shown by * $p < 0.05$; ** $p < 0.01$ by analysis of variance. For details of methods used see references [1] and [9].
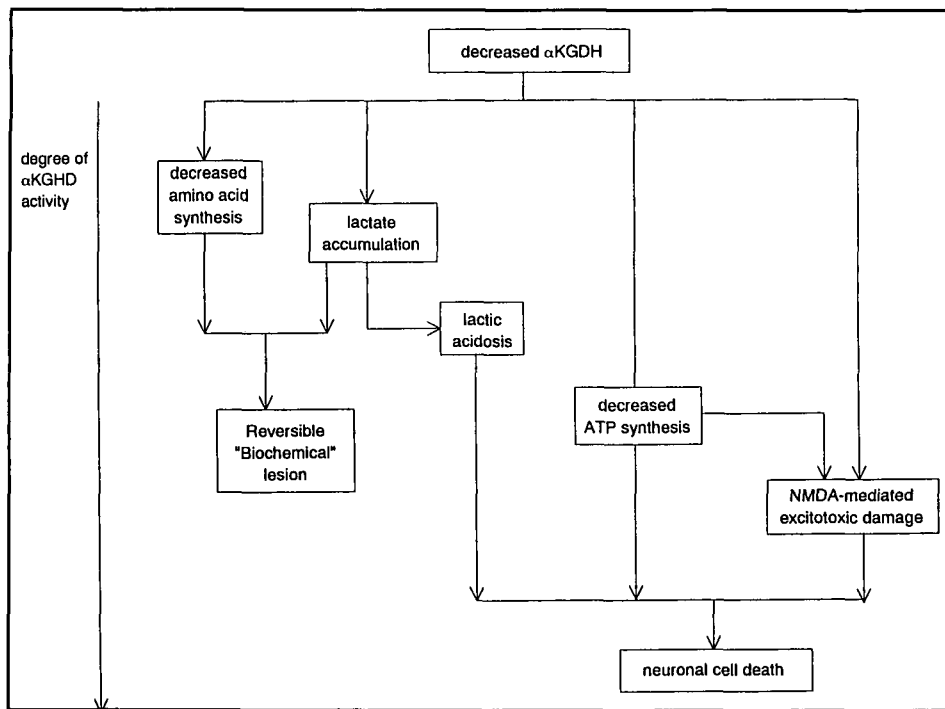
Figure 3 — Possible pathophysiological mechanisms involved in the biochemical lesion and ultimate neuronal cell loss in pyrithiamine-induced thiamine deficiency.

cerebellar damage have not been studied. Possible pathophysiological mechanisms implicated in neuronal cell death in WKS are shown schematically in Figure 3.

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