VITAMIN B1 (THIAMIN) AND ITS CHARACTERISTICS

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ABSTRACT

Vitamins are chemical compounds that play essential roles in crucial metabolic pathways in all living organisms. Thiamine, also known as vitamin B, was the first B vitamin to be discovered. It acts as a cofactor for numerous enzymes involved in energy metabolism. These thiamine-dependent enzymes are vital for the synthesis of neurotransmitters, the production of substances that protect against oxidative stress, and the creation of pentoses, which are essential precursors for nucleic acids. Thiamine holds a significant position in cerebral metabolism. Insufficient levels of thiamine result in dry and wet beriberi, which manifest as peripheral neuropathy and cardiomyopathy accompanied by edema and lactic acidosis. Additionally, it can lead to Wernicke Korsakoff syndrome.

Keywords: Vitamin B1, thiamine, Thiamin pyrophosphate, dry beriberi, wet beriberi, Wernicke-Korsakoff syndrome

1. Introduction

Vitamin B1 and its characteristics

The history of Vitamin B1

At one time, the disease beriberi was believed to be caused by a microorganism or toxin. The first indication of a nutritional an etiology was the virtual elimination of beriberi in the Japanese

Navy in 1885, brought about by increasing the proportion of meat and vegetables in the staple rice diet. In 1890, Eijkman, a Dutch medical officer stationed in Java, discovered that feeding chickens on polished rice induced a polyneuritis closely resembling human beriberi, which could be prevented by the addition of rice bran to the avian diet. A few years later, Grijns extracted a water-soluble 'polyneuritis preventive factor' from rice bran and correctly concluded that beriberi is the result of a dietary lack of an essential nutrient. By 1926, two Dutch chemists, Jansen and Donath, succeeded in isolating the factor (now called vita-min B1) in crystalline form from rice bran extracts. By 1936, Robert R. Williams had elucidated the structure of vitamin B1, which he named 'thiamine', and accomplished its synthesis. The failure of thiamin-deficient pigeons to metabolize pyruvate led Sir Rudolph Peters and his colleagues in the early 1930s to establish the essential role of thiamin in pyruvate metabolism. Lohmann and Schuster then discovered that the active coenzyme form of the vitamin was the di phosphate ester. (In this text, 'thiamin', rather than 'thiamine', is used in accordance with the nomenclature policy of the International Union of Nutritional Sciences Committee on Nomenclature.) [1]

2 Structure of Vitamin B1 or Thiamine activity

The thiamin molecule comprises substituted pyrimidine and Thiazole moieties linked by a methylene bridge Fig. (1.2). It is a quaternary amine, which exists as a monovalent or divalent cation depending on the pH of the solution. Three phosphorylated forms of thiamin occur in nature. In living tissues the pre-dominant form is the di phosphate, usually referred to as thiamin pyrophosphate (TPP) Fig. (1.2), which serves as a coenzyme in several metabolic pathways. Small amounts of the monophosphate and triphosphate esters also occur in animal tissues. Thiamin triphosphate has no coenzyme function, but it has a role (not yet completely understood) in nerve trans-mission. Thiamin monophosphate appears to be biologically in active. The name thiamin and the individual phosphates of thiamin will be used as specific terms; total thiamin means the sum of thiamin and its phosphates, and vitamin B1 is a non-specific generic term.[1]

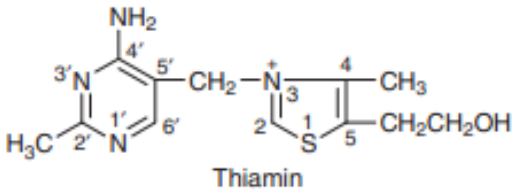

Fig.1 Chemical Structures of thiamin

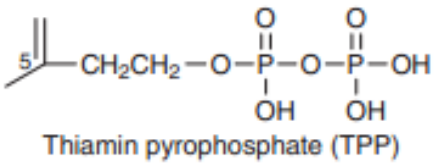

Fig.2 Chemical Structures of thiamin pyro phosphate

3 Dietary Sources

All plant and animal tissues contain vitamin B1and so the vitamin is existing in all natural unprocessed foods. Rich sources of vitamin B1 include yeast and yeast extract, wheat bran, oatmeal, whole-grain cereals, pulses, nuts, lean pork, heart, kidney and liver. Beef, lamb, chicken, eggs, vegetables and fruits contain intermediate amounts, while milk contains a relatively low amount. The milling of cereals removes most of the vitamin B1, so white flour, breakfast cereals and, in certain countries, polished rice are enriched by addition of the vitamin.

In most animal tissues, over 90% of the thiamin is phosphorylated, with TPP predominating. Exceptions are pig skeletal muscle [2] and chicken skeletal white muscle [3], in which the triphosphate constitutes 70–80% of the total thiamin existent. The natural vitamin B1 content of most cereals and cereal products, including white flour made from wheat, is present almost entirely in the form of non-phosphorylated thiamin.

signs of acute vitamin B1 deficiency that was not attributable to mal absorption. When biopsy samples from this patient were studied, the saturable component of thiamin uptake was found to be higher than in samples from non-deficient patients. The higher rate of uptake was reflected by an increased V_{max}, signifying up-regulation of thiamin carriers. The results from this one patient suggest that vitamin B1 deficiency in humans may enhance the capacity of thiamin absorption, an adaptive mechanism which has been reported in rats [4].

3.1 Absorption of bacterially synthesized thiamin in the large intestine

Instillation of thiamin directly into the colonic lumen of human subjects did not result in increased plasma concentrations of thiamin in blood samples taken 1, 2 and 4 hours after administration [5]. Based on this observation, it appears that bacterially synthesized thiamin is not absorbed in the large intestine. Kasper [6] pointed out that the intestinal flora destroys or utilizes a large part of the thiamin injected into the large intestine, and so the true capacity of the colon to absorb B vitamins can be determined only after eliminating the intestinal flora.

3.2 Post-absorptive metabolism

Following absorption, vitamin B1 is carried by the portal blood to the liver. Both non-phosphorylated thiamin and thiamin monophosphate circulate in the bloodstream, the former bound to plasma proteins. In normal adults, 20–30% of total thiamin in the plasma is protein-bound [7].

Transport of thiamin at the membrane level in rat liver has been studied using capacity thiamin/H^+ antiport mechanism was shown to be present with a narrow substrate specificity that was distinct from N1-methylnicotinamide/H^+ exchange.

Within the liver and in other tissues, thiamin is converted to its coenzyme form, TPP, by the catalytic action of thiamin pyro phospho kinase:

Thiamin + ATP → Thiamin Pyro Phosphate + AMP (1)

In the brain and other nervous tissue, some of the TPP is converted to thiamin triphosphate (TTP) by thiamin pyrophosphate ATP phosphoryl transferase:

Thiamin Pyro Phosphate + ATP → TTP + ADP (2)

Nervous tissue also contains thiamin pyrophosphatase converts small amounts of TPP to thiamin monophosphate (TMP) and inorganic phosphate:

Thiamin Pyro Phosphate → TMP + PPi (3)

Also in nervous tissue, TTP may be hydrolysed by thiamin triphosphatase to yield TPP and inorganic phosphate.

TTP → Thiamin Pyro Phosphate + PPi (4)

Similarly, in nervous tissue, TMP may hydrolyzed to thiamin by thiamin monophosphates.

TMP → thiamin + PPi (5)

The human body contains approximately 30 mg of total thiamin, of which approximately 80% is TPP, 10% is thiamin triphosphate, and the rest is thiamin monophosphate and free thiamin. About half of the body content of total thiamin is found in skeletal muscles, the remainder being distributed mainly in the liver, heart, kidney and brain. The biological half-life of [14C] thiamin in the body is 9 to 18 days. Because of this relatively high turnover rate and low storage.

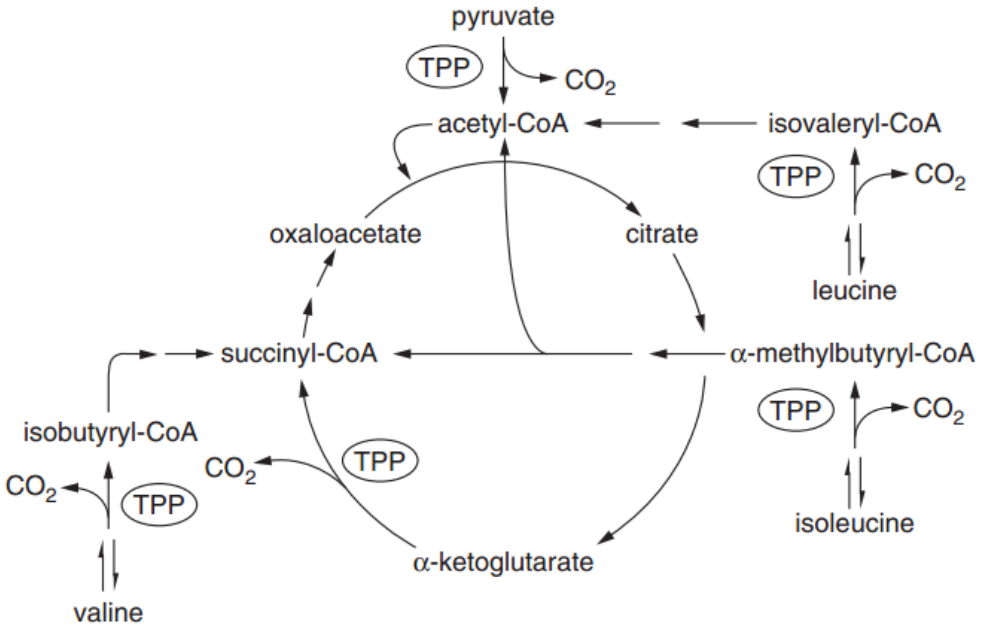

Fig. 3 Involvement of thiamin pyrophosphate (TPP) in the tri carboxylic acid cycle.

In mammalian tissues, TPP is a coenzyme for three mitochondrial enzymes involved in the oxidative decarboxylation of αketo acids; these enzymes are the pyruvate dehydrogenase complex (EC 1.2.4.1), α-ketoglutarate dehydrogenase (EC 1.2.4.2) and branched-chain α-keto acid dehydrogenase (EC 1.2.4.4). The involvement of these dehydrogenases in the tri carboxylic acid cycle is shown in Fig. 3. In addition, TPP is a coenzyme for transketolase (EC 2.2.1.1), which is found in the cytosol. [1].

3.3 Overview

There is increasing evidence that vitamin B1specifically thiamin triphosphate, is somehow involved in nerve membrane function. This property appears to be independent of the known coenzyme role of TPP. The evidence is substantiated by the finding that thiamin triphosphate, which accounts for 1% of total thiamin in rat brain, makes up 90% of total thiamin in the electric organ of the electric eel [8]. In the lamb, vitamin B1deprivation for 4 weeks led to a 20% depletion of total thiamin in the brain, with a similar percentage loss of free thiamin, thiamin monophosphate and TPP. There was, however, no appreciable fall in thiamin triphosphate [9].

Most of the vitamin B1 present in the brain and peripheral nerves is in the coenzyme form, TPP. The 1% or so of thiamin triphosphate is existing in whole brain and largely concentrated in the membrane fraction [10]. Fluorescence microscopy shows that the vitamin is localized in the membranes of peripheral nerves rather than in the axoplasm

[11]. A complete set of enzymes catalyzing the interconversion of thiamin and its phosphate esters has been isolated and purified from nervous tissue [12]. As discussed in the following, vitamin B1 may play a direct role in nerve conduction or it may be implicated in nerve transmission.

4 Vitamin B1 deficiency

4.1 Causes and effects

A deficiency of vitamin B1 may occur in situations of poor diet, chronic alcoholism, excessive diarrhoea or vomiting, malabsorption and genetic metabolic defects. Overloading the tissues with glucose without adequate thiamin coverage can precipitate deficiency, as can the use of diuretics. Diseases in which the metabolic rate is elevated (e.g. hyperthyroidism) can also lead to deficiency. Some researchers have demonstrated that secondary deficiency of a particular B-group vitamin can be induced by excessive dosing with another vitamin of this group. On the other hand, deficiencies in vitamins B6 and B12 induced vitamin B1 deficiency in rats, even when dietary thiamin levels were normal [13]. Howard [14].confirmed that folate deficiency in rats impairs thiamin absorption.

In humans, a lack of vitamin B1 has widespread effects, causing anorexia and associated weight loss, gastrointestinal disturbances, peripheral and central neuropathy, muscle weakness, and cardiovascular irregularities. With severe vitamin B1 deprivation, mental changes develop such as loss of emotional control, paranoid trends, manic or depressive episodes and confusion. The classic disease resulting from a gross deficiency of vitamin B1 in humans is promptly reversed by the administration of 5–10 μg of thiamin. If no more thiamin is given, severe signs reappear in 3–6 days. Pathological examination of the nervous systems of rats which experienced several bouts of deficiency disclosed anatomical lesions of certain parts of the brain. The lesions consisted of areas of tissue destruction and a marked proliferation of glial cells.

Within the center of lesions all modulated nerve fibers were destroyed [15]. Experimental vitamin B1 deficiency is produced more rapidly (12–16 days) and more effectively by the use of Pyrithiamin, a direct antagonist of TPP that also crosses the blood–brain barrier.

When [14C] glutamate was injected into the brains of vitamin B1-deficient rats, the specific radioactivity of GABA in the brains rose by 45–50%, suggesting a considerable increase in GABA shunt activity [16]. This increase in brain GABA level may explain the anorexia observed in vitamin B1-deficient rats. GABA aminotransferase, the enzyme principally responsible for GABA catabolism, is selectively inhibited by 1-(n-decyl)-3-

pyrazolidinone. When this inhibitor was administered to rats, brain GABA levels were increased three-fold and anorexia was observed in the absence of other symptoms [17].This finding is consistent with speculations that GABA is implicated in appetite-controlling mechanisms [18].

Human studies

The combined results from the several human studies have shown that inducement of vitamin B1 deficiency in adults produces a wide range of disorders involving the gastrointestinal tract, central and peripheral nervous systems, and cardiovascular system. Anorexia is a constant finding. Indigestion results from hypochlorhydria. Gastric atony results in severe constipation through lack of gut motility. Thus, when a barium meal is given, there is incomplete emptying of the stomach and pooling of the barium in segments of the small intestine, producing the so-called stepladder pattern. Changes in mood are an outstanding finding. There are paresthesia as with a stocking or glove type distribution, and impairment in perception of light, touch, pin prick, temperature and vibratory sensation. Subjects experience difficulty in rising from a squatting position owing to weakness of the calf muscles. The deep tendon reflexes (patella and Achilles) disappear after a while.

Electrocardiograms show irregularities, and subjects complain of shortness of breath, consciousness of the heartbeat, irregularities in heart rhythm and discomfort in the chest after exertion.

Biochemical changes include increased concentrations of pyruvate and lactate in the blood, particularly after exercise or the administration of glucose. Severe lactic acidosis can be life threatening.

4.2 Beriberi

The development of beriberi, its symptoms and its pathology are extremely variable, making it difficult to describe a clinical picture or sequence of development. Many of the early writers described three forms of beriberi in adult humans: dry (wasting) and wet (edematous) beriberi, which are chronic forms, and acute, fulminating (cardiac) beriberi. Which of these forms predominates depends on the circumstances. Vitamin B1 deprivation accompanied by malnutrition and low physical activity tends to favor beriberi presenting in the dry form, whereas high carbohydrate intake and high physical activity during vitamin B1 deprivation predispose to wet beriberi. It should be emphasized that any one of these forms may merge into another [1].

Dry beriberi is a disease of the peripheral nervous system involving bilateral impairment of sensory, motor and reflex functions. The pathological findings are segmental thinning of

myelin in peripheral nerves, progressing to degeneration of fiber tracts. The neuropathy begins in the feet and legs and then extends up the body. Early signs of dry beriberi often include sensations of pins and needles and numbness in the feet. The legs, especially the calves, feel heavy and weak so that walking becomes uncomfortable. As the disease progresses, there is a marked wasting of the leg muscles and even slight pressure applied to the calves elicits severe pain. The characteristic foot and wrist drop develop and there may be complete flaccid paralysis of the lower, and occasionally upper, extremities.

In wet beriberi, vitamin B1 deficiency affects the cardiovascular system by causing arteriolar dilation throughout the circulatory system and by weakening the heart muscle. The vasodilation causes a two-fold increase in the venous return of blood to the heart. Physical signs of wet beriberi are indicative of high-output cardiac failure; they include tachycardia, rapid Wernicke Korsakoff syndrome. Thus, for example, the nystagmus is due to damage of the sixth cranial nerve; the ataxia is related to loss of neurons in the superior vermis of the cerebellum; and the amnesia is associated with atrophy of the mammillary bodies.

Although the Wernicke–Korsakoff syndrome results from a lack of dietary vitamin B1, two clinical observations suggest that genetic factors are important in its pathogenesis: it develops in only a small majority of alcoholics and other chronically malnourished persons, and it occurs much more frequently among Europeans than among Asians [1].

The possibility of a genetic effect was investigated by [19]. who found that transketolase in tissue-cultured cells from patients with Wernicke–Korsakoff syndrome was abnormal in that the binding of TPP to the Apo-enzyme was diminished. The abnormal-ity persisted through more than 20 generations of culture in medium containing excess thiamin and no ethanol, and therefore appeared to be genetic rather than dietary. Thus the abnormal enzyme appears to be a structural mutant. Persistent aberrations had previously been found in erythrocyte transketolase from these patients, even after they had been treated with thiamin for months while in hospital. The abnormality appeared to be specific for transketolase as pyruvate dehydrogenase and α-ketoglutarate dehydrogenase were unaffected.

Because the symptoms of Wernicke's disease can be alleviated following the administration of thiamin, the abnormal transketolase is presumably clinically unimportant if the diet is adequate. This type of genetic abnormality is an example of an inborn predisposition to metabolic disorders. Unlike inborn errors of metabolism, inborn predispositions are likely to be clinically silent unless the person with the predisposition faces an

appropriate stress. In cases of Wernicke–Korsakoff syndrome, the stress is a deficiency of vitamin B1 [20]. demonstrated a highly significant association between a particular variant of erythrocyte transketolase and the Wernicke–Korsakoff syndrome, supporting the concept that the syndrome has a genetic as well as a dietary origin.

4.3 Treatment of beriberi

Beriberi is treated with a proprietary thiamin preparation, the dosage and route depending on the patient's condition. To prevent further recurrences, a good diet containing all of the B-group vitamins should be instituted. Severe cardiac (shoshin) Beriberi and Wernicke–Korsakoff syndrome constitute medical emergencies requiring immediate treatment with thiamin, given intravenously. Treatment of Wernicke–Korsakoff syndrome will eradicate the symptoms of encephalopathy (with abstinence of alcohol), but the psychosis is irreversible.

Effects of high intake

Thiamin is non-toxic by the oral route because excess amounts of ingested thiamin are rapidly excreted in the urine. Large parenteral doses of thiamin administered over a long period have been reported to pro-duce clinical manifestations and, in some cases, even death [21].

TABLE 1 Comparison of Recommended Dietary Allowances for thiamin and "Reference Daily Intake" (RDI) Currently Used in Nutritional Labeling in the United States [22].

Category	Age (years)	Vitamine B1 or Thiamin
Infants	0.0-0.5	0.3
	0.5-1.0	0.4
Children	1-3	0.7
	4-6	0.9
	7-10	1.0
Males	11-14	1.3
	15-18	1.5
	19-24	1.5
	25-50	1.5
	51+	1.2
Females	11-14	1.1

	15-18	1.1
	19-24	1.1
	25-50	1.1
	51+	1.0

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