

THIAMINE: AN OVERVIEW

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Summary

Thiamine or thiamin, sometimes called aneurin, is a water-soluble vitamin of the B complex (vitamin B₁), whose phosphate derivatives are involved in many cellular processes. The best characterized form is thiamine pyrophosphate (ThDP), a coenzyme in the catabolism of sugars and amino acids. The present review states the dreadful diseases caused due to deficiency of Thiamine such as Beri- beri, Alcoholic brain disease, HIV-AIDS, Idiopathic paralytic disease in wild birds and Genetic diseases etc. The present review also states the, biosynthesis, absorption, its various derivatives with its functions and research which is been carried out.

Keywords: Beri- Beri, Polyneuritis, Thiamine, Vitamin B₁.

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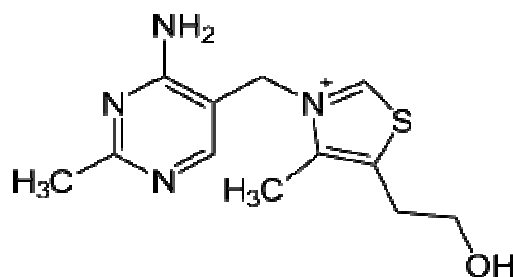
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Introduction

Thiamine or thiamin,¹ sometimes called aneurin, is a water-soluble vitamin of the B complex (vitamin B₁), whose phosphate derivatives are involved in many cellular processes. The best characterized form is thiamine pyrophosphate (ThDP), a coenzyme in the catabolism of sugars and amino acids. In yeast, ThDP is also required in the first step of alcoholic fermentation. Thiamine is synthesized in bacteria, fungi and plants. Animals must cover all their needs from their food and insufficient intake results in a disease called beriberi affecting the peripheral nervous system (polyneuritis) and/or the cardiovascular system, with fatal outcome if not cured by thiamine administration.² In less severe deficiency, nonspecific signs include malaise, weight loss, irritability and confusion.³ Today, there is still a lot of work devoted to elucidating the exact mechanisms by which thiamine deficiency leads to the specific symptoms observed. Finally, new thiamine phosphate derivatives have recently been discovered,⁴ emphasizing the complexity of thiamine metabolism and the need for more research in the field.



History

Thiamine was the first of the water-soluble vitamins to be described,² leading to the discovery of more such trace compounds essential for survival and to the notion of vitamin. Chinese medical texts referred to beriberi (a thiamine deficiency disease) as early as 2700 BC.⁵ It was not until AD 1884 that Kanehiro Takaki (1849-1920), a surgeon general in the Japanese navy, rejected the previous germ theory and attributed the disease to insufficient nitrogen intake (protein deficiency). In 1897 Christiaan Eijkman (1858-1930), a military doctor in the Dutch Indies, discovered that fowl fed on a diet of cooked, polished rice developed paralysis, which could be reversed by discontinuing rice polishing.⁶ He attributed that to a nerve poison in the endosperm of rice, from which the outer layers of the grain gave protection to the body. Eijkman was awarded the Nobel Prize in Physiology and Medicine in 1929, because his observations led to the discovery of vitamins. An associate, Gerrit Grijns (1865-1944), correctly interpreted the connection between excessive consumption of polished rice and beriberi in 1901: he concluded that rice contained an essential nutrient in the outer layers of the grain that was removed by polishing.⁷ In 1911 Casimir Funk isolated an antineuritic substance from rice bran that he called a "vitamine" (on account of its containing an amino group).⁸ Thiamine ("sulfur-containing vitamin") was synthesized in 1936 by the same group.⁹ It was first named "aneurin" (for anti-neuritic vitamin).¹⁰ Sir Rudolph Peters, in Oxford, introduced thiamine-deprived pigeons as a

model for understanding how thiamine deficiency can lead to the pathological-physiological symptoms of beriberi. Indeed, feeding the pigeons upon polished rice leads to an easily recognizable behavior of head retraction, a condition called opisthotonos. As no morphological modifications were observed in the brain of the pigeons before and after treatment with thiamine, Peeters introduced the concept of biochemical lesion¹¹ When Lohman and Schuster (1937) showed that the diphosphorylated thiamine derivative (thiamine diphosphate, ThDP) was a cofactor required for the oxydative decarboxylation of pyruvate,¹² (a reaction now known to be catalyzed by pyruvate dehydrogenase), the mechanism of action of thiamine in the cellular metabolism seemed to be elucidated. Presently, this view seems to be oversimplified: pyruvate dehydrogenase is only one of several enzymes requiring thiamine diphosphate as a cofactor, moreover other thiamine phosphate derivatives have been discovered since then, and they may also contribute to the symptoms observed during thiamine deficiency.¹³

Chemical properties

Thiamine is a colorless compound with a chemical formula $C_{12}H_{17}N_4OS$. Its structure contains a pyrimidine ring and a thiazole ring linked by a methylene bridge. Thiamine is soluble in water, methanol, and glycerol and practically insoluble in acetone, ether, chloroform, and benzene. It is stable at acidic pH, but is unstable in alkaline solutions.^{2, 14} Thiamine is unstable to heat, but stable during frozen storage. It is unstable when exposed to ultraviolet light¹⁴ and gamma irradiation.^{15, 16} Thiamine reacts strongly in Maillard-type reactions.²

Biosynthesis

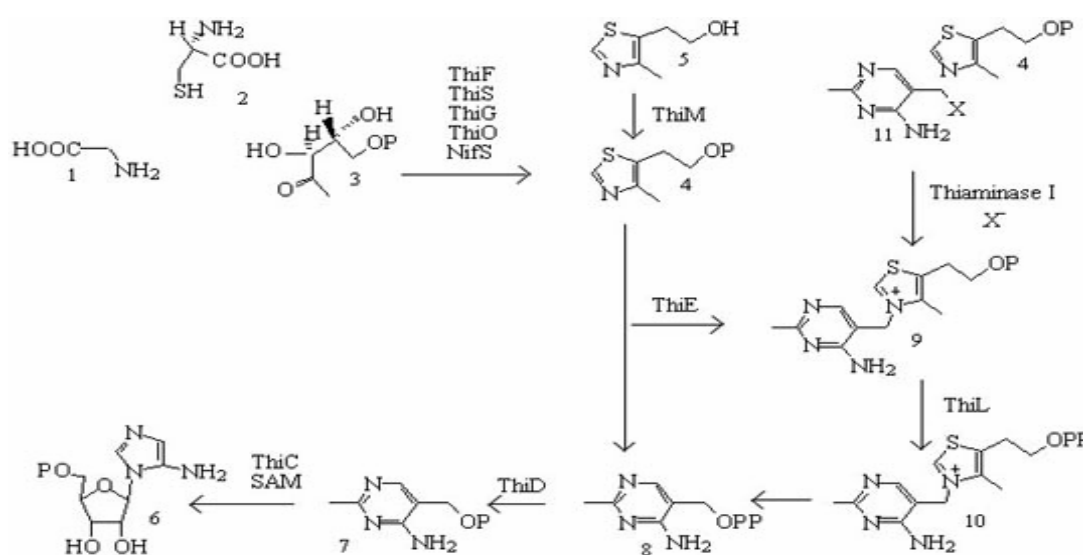


Figure 1: Biosynthesis of Thiamine

Absorption and transport

Absorption

Thiamine is released by the action of phosphates and pyrophosphates in the upper small intestine. At low concentrations the process is carrier mediated and at higher concentrations, absorption occurs via passive diffusion. Active transport is greatest in the jejunum and ileum (it is inhibited by alcohol consumption and by folic deficiency).² Decline in thiamine absorption occurs at intakes above 5 mg.¹⁷ The cells of the intestinal mucosa have thiamine pyrophosphokinase activity, but it is unclear whether the enzyme is linked to active absorption. The majority of thiamine present in the intestine is in the pyrophosphorylated form ThDP, but when thiamine arrives on the serosal side of the intestine it is often in the free form. The uptake of thiamine by the mucosal cell is likely coupled in some way to its phosphorylation/dephosphorylation. On the serosal side of the intestine, evidence has shown that discharge of the vitamin by those cells is dependent on Na⁺-dependent ATPase.³

Bound to serum proteins

The majority of thiamine in serum is bound to proteins, mainly albumin. Approximately 90% of total thiamine in blood is in erythrocytes. A specific binding protein called thiamine-binding protein (TBP) has been identified in rat serum and is believed to be a hormonally regulated carrier protein that is important for tissue distribution of thiamine.³ Cellular uptake of thiamine by cells of the blood and other tissues occurs via active transport and passive diffusion.² About 80% of intracellular thiamine is phosphorylated and most is bound to proteins. In some tissues, thiamine uptake and secretion appears to be mediated by a soluble thiamine transporter that is dependent on Na⁺ and a transcellular proton gradient.³

Tissue distribution

Human storage of thiamine is about 25 to 30 mg with the greatest concentrations in skeletal muscle, heart, brain, liver, and kidneys. ThMP and free (unphosphorylated) thiamine is present in plasma, milk, cerebrospinal fluid, and likely all extracellular fluids. Unlike the highly phosphorylated forms of thiamine, ThMP and free thiamine are capable of crossing cell membranes. Thiamine contents in human tissues are less than those of other species.^{3, 18}

Excretion

Thiamine and its acid metabolites (2-methyl-4-amino-5-pyrimidine carboxylic acid, 4-methyl-thiazole-5-acetic acid and thiamine acetic acid) are excreted principally in the urine.¹⁴

Thiamine phosphate derivatives and function

Thiamine is mainly the transport form of the vitamin, while the active forms are phosphorylated thiamine derivatives. There are four known natural thiamine phosphate derivatives: thiamine

monophosphate (ThMP), thiamine diphosphate (ThDP), also sometimes called thiamine pyrophosphate (TPP), thiamine triphosphate (ThTP), and the recently discovered adenosine thiamine triphosphate (AThTP) and adenosine thiamine diphosphate (AThDP).¹⁹

Thiamine monophosphate

There is no known physiological role of ThMP.

Thiamine diphosphate

The synthesis of thiamine diphosphate (ThDP), also known as *thiamine pyrophosphate* (TPP) or *coccarboxylase*, is catalyzed by an enzyme called thiamine diphosphokinase according to the reaction $\text{thiamine} + \text{ATP} \rightarrow \text{ThDP} + \text{AMP}$ (EC 2.7.6.2).²⁰ ThDP is a coenzyme for several enzymes that catalyze the transfer of two-carbon units and in particular the dehydrogenation (decarboxylation and subsequent conjugation with coenzyme A) of 2-oxoacids (alpha-keto acids). Examples include:

Present in most species

pyruvate dehydrogenase and 2-oxoglutarate dehydrogenase (also called α -ketoglutarate dehydrogenase) branched-chain α -keto acid dehydrogenase 2-hydroxyphytanoyl-CoA lyase transketolase

Present in some species:

pyruvate decarboxylase (in yeast) , several additional bacterial enzymes

The enzymes transketolase, pyruvate dehydrogenase (PDH) and 2-oxoglutarate dehydrogenase (OGDH) are all important in carbohydrate metabolism.²¹ The cytosolic enzyme transketolase is a key player in the pentose phosphate pathway, a major route for the biosynthesis of the pentose sugars deoxyribose and ribose.²² The mitochondrial PDH and OGDH are part of biochemical pathways that result in the generation of adenosine triphosphate (ATP), which is a major form of energy for the cell. PDH links glycolysis to the citric acid cycle, while the reaction catalyzed by OGDH is a rate-limiting step in the citric acid cycle.²³ In the nervous system, PDH is also involved in the production of acetylcholine, a neurotransmitter, and for myelin synthesis.²⁴ Thiamine triphosphate. Thiamine triphosphate (ThTP) was long considered a specific neuroactive form of thiamine. However, recently it was shown that ThTP exists in bacteria, fungi, plants and animals suggesting a much more general cellular role.²⁵ In particular in *E. coli*, it seems to play a role in response to amino acid starvation.²⁶

Adenosine thiamine triphosphate

Adenosine thiamine triphosphate (A_{Th}TP) or thiaminylated adenosine triphosphate has recently been discovered in *Escherichia coli* where it accumulates as a result of carbon starvation.^[4] In *E. coli*, A_{Th}TP may account for up to 20 % of total thiamine. It also exists in lesser amounts in yeast, roots of higher plants and animal tissue.²⁷

Adenosine thiamine diphosphate

Adenosine thiamine diphosphate (A_{Th}DP) or thiaminylated adenosine diphosphate exists in small amounts in vertebrate liver, but its role remains unknown.²⁷

Deficiency

Thiamine derivatives and thiamine-dependent enzymes are present in all cells of the body, thus, a thiamine deficiency would seem to adversely affect all of the organ systems. However, the nervous system and the heart are particularly sensitive to thiamine deficiency, because of their high oxidative metabolism. Thiamine deficiency can lead to severe fatigue of eyes and myriad problems including neurodegeneration, wasting and death. A lack of thiamine can be caused by malnutrition, a diet high in thiaminase-rich foods (raw freshwater fish, raw shellfish, ferns) and/or foods high in anti-thiamine factors (tea, coffee, betel nuts)²⁸ and by grossly impaired nutritional status associated with chronic diseases, such as alcoholism, gastrointestinal diseases, HIV-AIDS, and persistent vomiting.²⁹ It is thought that many people with diabetes have a deficiency of thiamine and that this may be linked to some of the complications that can occur.³⁰
³¹ Well-known syndromes caused by thiamine deficiency include beriberi and Wernicke-Korsakoff syndrome, diseases also common with chronic alcoholism.

Beriberi	<p>Beriberi is a neurological and cardiovascular disease. The three major forms of the disorder are dry beriberi, wet beriberi, and infantile beriberi.¹⁴</p> <ul style="list-style-type: none"> • Dry beriberi is characterized principally by peripheral neuropathy consisting of symmetric impairment of sensory, motor, and reflex functions affecting distal more than proximal limb segments and causing calf muscle tenderness.²⁹ • Wet beriberi is associated with mental confusion, muscular wasting, edema, tachycardia, cardiomegaly, and congestive heart failure in addition to peripheral neuropathy.² • Infantile beriberi occurs in infants breast-fed by thiamin-deficient mothers (who may show no sign of thiamine deficiency). Infants may manifest cardiac, aphonic, or pseudomeningitic forms of the disorder. Infants with cardiac beriberi frequently exhibit a loud piercing cry, vomiting, and tachycardia.¹⁴ Convulsions are not uncommon, and death may ensue if thiamine is not administered promptly.²⁹ <p>Following thiamine treatment, rapid improvement occurs generally within 24 hours.¹⁴ Improvements of peripheral neuropathy may require several months of thiamine treatment.³²</p>
Alcoholic brain disease	<p>Nerve cells and other supporting cells (such as glial cells) of the nervous system require thiamine. Examples of neurologic disorders that are linked to alcohol abuse include Wernicke's encephalopathy (WE, Wernicke-Korsakoff syndrome) and Korsakoff's psychosis (alcohol amnesic disorder) as well as varying degrees of cognitive impairment.³³</p>
Wernicke's encephalopathy	<p>Is the most frequently encountered manifestation of thiamine deficiency in Western society, though it may also occur in patients with impaired nutrition from other causes, such as gastrointestinal disease,³⁴ those with HIV-AIDS, and with the injudicious administration of parenteral glucose or hyperalimentation without adequate B-vitamin supplementation.³⁵ This is a striking neuro-psychiatric disorder characterized by paralysis of eye movements, abnormal stance and gait, and markedly deranged mental function.³⁶</p> <p>Alcoholics may have thiamine deficiency because of the following:</p> <p>Inadequate nutritional intake: alcoholics tend to intake less than the recommended amount of thiamine.</p>

	<p>Decreased uptake of thiamine from the GI tract: active transport of thiamine into enterocytes is disturbed during acute alcohol exposure.</p> <p>Liver thiamine stores are reduced due to hepatic steatosis or fibrosis.³⁷</p> <p>Impaired thiamine utilization: magnesium, which is required for the binding of thiamine to thiamine-using enzymes within the cell, is also deficient due to chronic alcohol consumption. The inefficient utilization of any thiamine that does reach the cells will further exacerbate the thiamine deficiency.</p> <p>Ethanol per se inhibits thiamine transport in the gastrointestinal system and blocks phosphorylation of thiamine to its cofactor form (ThDP).³⁸</p>
Korsakoff Psychosis	<p>Is generally considered to occur with deterioration of brain function in patients initially diagnosed with WE.³⁹ This is an amnesic-confabulatory syndrome characterized by retrograde and anterograde amnesia, impairment of conceptual functions, and decreased spontaneity and initiative.²⁹ Following improved nutrition and the removal of alcohol consumption, some impairments linked with thiamine deficiency are reversed; particularly poor brain functionality, although in more severe cases, Wernicke-Korsakoff syndrome leaves permanent damage.</p>
In Poultry	<p>As most feedstuffs used in poultry diets contain enough quantities of vitamins to meet the requirements in this species, deficiencies in this vitamin does not occur with commercial diets. This was, at least, the opinion in the 1960s.⁴⁰ Mature chickens show signs 3 weeks after being fed a deficient diet. In young chicks, it can appear before 2 weeks of age. Onset is sudden in young chicks. There is anorexia and an unsteady gait. Later on, there are locomotor signs, beginning with an apparent paralysis of the flexor of the toes. The characteristic position is called "stargazing", meaning a chick "sitting on its hocks and the head in opisthotonos. Response to administration of the vitamin is rather quick, occurring a few hours later.⁴¹ A therapeutic diagnosis can be tried by supplementing Vitamin B₁ only in the affected bird. If the animals do not respond in a few hours, Vitamin B₁ deficiency can be excluded.⁴²</p>
In ruminants	<p>Polioencephalomalacia (PEM), is the most common thiamine deficiency disorder in young ruminant and nonruminant animals. Symptoms of PEM include a profuse, but transient diarrhea, listlessness, circling movements, star gazing or opisthotonus (head drawn back over neck), and muscle tremors.⁴³ The most common cause is high-carbohydrate feeds, leading to the overgrowth of thiaminase-producing bacteria, but dietary ingestion of thiaminase (e.g. in bracken fern), or inhibition of thiamine absorption by high sulfur intake are</p>

	also possible. ⁴⁴
Idiopathic paralytic disease in wild birds	Recently thiamine deficiency has been identified as the cause of a paralytic disease affecting wild birds in the Baltic Sea area dating back to 1982. ⁴⁵ In this condition, there is difficulty in keeping the wings folded along the side of the body when resting, loss of the ability to fly and voice with eventual paralysis of the wings and legs and death. It affects primarily 0.5–1 kg sized birds such as the herring gull (<i>Larus argentatus</i>), Common Starling (<i>Sturnus vulgaris</i>) and Common Eider (<i>Somateria mollissima</i>). Researches noted "Because the investigated species occupy a wide range of ecological niches and positions in the food web, we are open to the possibility that other animal classes may suffer from thiamine deficiency as well." ⁴⁵

Table 1: Deficiency of Thiamine**Analysis and diagnostic testing**

Oxidation of thiamine derivatives to fluorescent thiochromes by potassium ferricyanide under alkaline conditions. A positive diagnosis test for thiamine deficiency can be ascertained by measuring the activity of the enzyme transketolase in erythrocytes (Erythrocyte Transketolase Activation Assay).⁴⁶ Thiamine, as well as its phosphate derivatives, can also be detected directly in whole blood, tissues, foods, animal feed and pharmaceutical preparations following the conversion of thiamine to fluorescent thiochrome derivatives (Thiochrome Assay) and separation by high performance liquid chromatography (HPLC).^{47, 48} In recent reports, a number of Capillary Electrophoresis (CE) techniques and in-capillary enzyme reaction methods have emerged as potential alternative techniques for the determination and monitoring of thiamine in samples.⁴⁹

Genetic diseases

Genetic diseases of thiamine transport are rare but serious. Thiamine Responsive Megaloblastic Anemia with diabetes mellitus and sensorineural deafness (TRMA)⁵⁰ is an autosomal recessive disorder caused by mutations in the gene SLC19A2,⁵¹ a high affinity thiamine transporter. TRMA patients do not show signs of systemic thiamine deficiency, suggesting redundancy in the thiamine transport system. This has led to the discovery of a second high affinity thiamine transporter, SLC19A3.⁵² Leigh Disease (Subacute Necrotising Encephalomyelopathy) is an inherited disorder which affects mostly infants in the first years of life and is invariably fatal.⁵³ Pathological similarities between Leigh disease and WE led to the hypothesis that the cause was a defect in thiamine metabolism. One of the most consistent findings has been an abnormality of

the activation of the pyruvate dehydrogenase complex⁵⁴. Other disorders in which a putative role for thiamine has been implicated include Subacute Necrotizing Encephalomyelopathy, Opsoclonic Cerebellopathy (a paraneoplastic syndrome), and Nigerian Seasonal Ataxia. In addition, several inherited disorders of ThDP-dependent enzymes have been reported,⁵⁵ which may respond to thiamine treatment.²⁹

Research

Research in the field mainly concerns the mechanisms by which thiamine deficiency leads to neuronal death in relation to Wernicke Korsakoff Psychosis. Another important field concerns the understanding of the molecular mechanisms involved in ThDP catalysis. More recently, research has been devoted to the understanding of the possible non-cofactor roles of other derivatives such as ThTP and AThTP.⁵⁵ Understanding the mechanism by which thiamine deficiency leads to selective neuronal death. Experimentally induced beriberi polyneuropathy in chickens may be a good model for studying these forms of neuropathy in view of diagnosis and treatment.⁵⁶ From studies using rat models, a link between thiamine deficiency and colon carcinogenesis was suggested.⁵⁷ Rat model is used also in research of Wernicke's encephalopathy.⁵⁸ Thiamine deprived mice are a classic model of systemic oxidative stress, used in research of Alzheimer's disease.⁵⁹ Catalytic mechanisms in thiamine diphosphate-dependent enzymes. A lot of work is devoted to the understanding of the interplay between ThDP and ThDP-dependent enzymes in catalysis.⁶⁰

Non-cofactor roles of thiamine derivatives

Thiamine compounds other than ThDP exist in most cells from many organisms, including bacteria, fungi, plants and animals. Among those compounds are thiamine triphosphate (ThTP) and adenosine thiamine triphosphate (AThTP) are thought to have non-cofactor roles, though at present it is not known to what extent they participate in the symptoms.^{61, 62}

Persistent carbenes

The production of furoin from furfural is catalyzed by thiamine through a relatively stable carbene (organic radical). This reaction, studied in 1957 by R. Breslow, was the first evidence for the existence of persistent carbenes.⁶²

Conclusion

Thiamine is water soluble vitamin which evolves in various cellular processes in the body. It is a magic bullet to cure various dreadful diseases. The progress made in the past few years has been impressive and there is an emerging general consensus that thiamine therapies are a promising and novel approach to various diseases that could lead to effective interventions for the treatment of various diseases with minimal side effects.

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