Vitamin B1 (Thiamine)

Thiamine, also known as thiamin or vitamin B₁, is a vitamin found in food and used as a dietary supplement. As a supplement it is used to treat and prevent thiamine deficiency and disorders that result from it, including beriberi, Korsakoff's syndrome, and Korsakoff's psychosis. Other uses include maple syrup urine disease and Leigh's disease. It is taken by mouth or by injection.

Side effects are generally few. Allergic reactions including anaphylaxis may occur. Thiamine is in the B complex family. It is needed for the metabolism of carbohydrates. As people are unable to make it, thiamine is an essential nutrient. Food sources include whole grains, meat, and fish.

Thiamine was discovered in 1897, isolated in 1926, and first made in 1936. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system. Thiamine is available as a generic medication and over the counter. The wholesale cost in the developing world is about 2.17 USD per one gm vial. In the United States a month of replacement is less than 25 USD. Some countries require its addition to certain foods such as grains.

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Medical uses

Thiamine deficiency

Thiamine is used to treat thiamine deficiency which can prove fatal. In less-severe cases, nonspecific signs include malaise, weight loss, irritability and confusion.

Well-known syndromes caused by thiamine deficiency include beriberi, Wernicke-Korsakoff syndrome, and optic neuropathy.

Other uses

Other uses include maple syrup urine disease and Leigh's disease.
Side effects

Side effects are generally few.[1] Allergic reactions including anaphylaxis may occur.[1]

Chemistry

Thiamine is a colorless organosulfur compound with a chemical formula $\text{C}_{12}\text{H}_{17}\text{N}_4\text{O}$.[1] Its structure consists of an aminopyrimidine and a thiazole ring linked by a methylene bridge. The thiazole is substituted with methyl and hydroxyethyl side chains. Thiamine is soluble in water, methanol, and glycerol and practically insoluble in less polar organic solvents. It is stable at acidic pH, but is unstable in alkaline solutions.[7][9] Thiamine, which is a N-heterocyclic carbene, can be used in place of cyanide as a catalyst for benzoin condensation.[10] Thiamine is unstable to heat, but stable during frozen storage.[citation needed] It is unstable when exposed to ultraviolet light[9] and gamma irradiation.[11][12] Thiamine reacts strongly in Maillard-type reactions.[7]

Biosynthesis

Complex thiamine biosynthesis occurs in bacteria, some protozoans, plants, and fungi.[13][14] The thiazole and pyrimidine moieties are biosynthesized separately and then combined to form ThMP by the action of thiamine-phosphate synthase (EC 2.5.1.3). The biosynthetic pathways may differ among organisms. In E. coli and other enterobacteria, ThMP may...
be phosphorylated to the cofactor ThDP by a thiamine-phosphate kinase (ThMP + ATP → ThDP + ADP, EC 2.7.4.16). In most bacteria and in eukaryotes, ThMP is hydrolyzed to thiamine, which may then be pyrophosphorylated to ThDP by thiamine diphosphokinase (thiamine + ATP → ThDP + AMP, EC 2.7.6.2).

The biosynthetic pathways are regulated by riboswitches. If there is sufficient thiamine present in the cell then the thiamine binds to the mRNAs for the enzymes that are required in the pathway and prevents their translation. If there is no thiamine present then there is no inhibition, and the enzymes required for the biosynthesis are produced. The specific riboswitch, the TPP riboswitch, is the only riboswitch identified in both eukaryotic and prokaryotic organisms.[15]

Nutrition

Occurrence in foods

Thiamin is found in a wide variety of processed and whole foods, with edible seeds, legumes, rice and processed foods, such as breakfast cereals, having among the highest contents.[16][17]

The salt thiamin mononitrate, rather than thiamin hydrochloride, is used for food fortification, as the mononitrate is more stable, and does not absorb water from natural humidity (is non-hygroscopic), whereas thiamin hydrochloride is hygroscopic.[citation needed] When thiamin mononitrate dissolves in water, it releases nitrate (about 19% of its weight) and is thereafter absorbed as the thiamin cation.

Some other foods naturally rich in thiamin are corn flour, pork, pecans and spinach.[16][17]

Dietary Reference Intakes

The Food and Nutrition Board of the U.S. Institute of Medicine updated Estimated Average Requirements (EARs) and Recommended Dietary Allowances (RDAs) for thiamine in 1998. The current EARs for thiamine for women and men ages 14 and up are 0.9 mg/day and 1.0 mg/day, respectively; the RDAs are 1.1 and 1.2 mg/day. RDAs are higher than EARs so as to identify amounts that will cover people with higher than average requirements. RDA for pregnancy equals 1.4 mg/day. RDA for lactation equals 1.4 mg/day. For infants up to 12 months the Adequate Intake (AI) is 0.2-0.3 mg/day. and for children ages 1–13 years the RDA increases with age from 0.5 to 0.9 mg/day. As for safety, the Food and Nutrition Board of the U.S. Institute of Medicine sets Tolerable Upper Intake Levels (known as ULs) for vitamins and minerals when evidence is sufficient. In the case of thiamine there is no UL, as there is no human data for adverse effects from high doses. The European Food Safety Authority reviewed the same safety question and also reached the conclusion that there was not sufficient evidence to set a UL for thiamine.[18] Collectively the EARs, RDAs and ULs are referred to as Dietary Reference Intakes.[19]

For U.S. food and dietary supplement labeling purposes the amount in a serving is expressed as a percent of Daily Value (%DV). For thiamine labeling purposes 100% of the Daily Value was 1.5 mg, but as of May 2016 it has been revised to 1.2 mg. A table of the pre-change adult Daily Values is provided at Reference Daily Intake. Food and supplement companies have until July 28, 2018 to comply with the change.

Antagonists

Thiamine in foods can be degraded in a variety of ways. Sulfites, which are added to foods usually as a preservative,[20] will attack thiamine at the methylene bridge in the structure, cleaving the pyrimidine ring from the thiazole ring.[8] The rate of this reaction is increased under acidic conditions. Thiamine is degraded by thermolabile thiaminases (present in raw fish and shellfish).[7]. Some thiaminases are produced by bacteria. Bacterial thiaminases are cell surface enzymes that must dissociate from the membrane before being activated; the dissociation can occur in ruminants under acidic conditions. Rumen bacteria also reduce sulfate to sulfite, therefore high dietary intakes of sulfate can have thiamine-antagonistic activities.

Plant thiamine antagonists are heat-stable and occur as both the ortho- and para-hydroxyphenols. Some examples of these antagonists are caffeic acid, chlorogenic acid, and tannic acid. These compounds interact with the thiamine to oxidize the thiazole ring, thus rendering it unable to be absorbed. Two flavonoids, quercetin and rutin, have also been implicated as thiamine antagonists.[8]

Absorption and transport

Absorption

Thiamine is released by the action of phosphatase and pyrophosphatase 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; but, active transport can be inhibited by alcohol consumption and by folic deficiency.[7] Decline in thiamine absorption occurs at intakes above 5 mg/day.[21] The cells of the intestinal mucosa have thiamine pyrophosphokinase activity, but it is unclear as to 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.[8]

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 hormone-regulated carrier protein important for tissue distribution of thiamine.[8]

Cellular uptake

Uptake of thiamine by cells of the blood and other tissues occurs via active transport and passive diffusion.[7] The brain requires much more thiamine than other tissues of the body. Much of ingested thiamine never reaches the brain because of passive diffusion and the blood–brain barrier. 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.\textsuperscript{[8]}

### 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, it is presumed, 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.\textsuperscript{[8][22]}

### 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.\textsuperscript{[9]}

### Function

Its phosphate derivatives are involved in many cellular processes. The best-characterized form is thiamine pyrophosphate (TPP), a coenzyme in the catabolism of sugars and amino acids. In yeast, TPP is also required in the first step of alcoholic fermentation. All organisms use thiamine, but it is made only in bacteria, fungi, and plants. Animals must obtain it from their diet, and thus, for humans, it is an essential nutrient. Insufficient intake in birds produces a characteristic polyneuritis.

Thiamine is usually considered as the transport form of the vitamin. There are five 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). While the coenzyme role of thiamine diphosphate is well-known and extensively characterized, the non-coenzyme action of thiamine and derivatives may be realized through binding to a number of recently identified proteins which do not use the catalytic action of thiamine diphosphate.\textsuperscript{[23]}

### Thiamine diphosphate

No physiological role is known for ThMP; however, the diphosphate is physiologically relevant. The synthesis of thiamine diphosphate (ThDP), also known as thiamine pyrophosphate (TPP) or cocarboxylase, is catalyzed by an enzyme called thiamine diphosphokinase according to the reaction thiamine + ATP → ThDP + AMP (EC 2.7.6.2). 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 \( \alpha \)-ketoglutarate dehydrogenase)
  - branched-chain \( \alpha \)-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. 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. 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. 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 (AThTP) or thiaminylated adenosine triphosphate has recently been discovered in Escherichia coli, where it accumulates as a result of carbon starvation.[27] In E. coli, AThTP may account for up to 20% of total thiamine. It also exists in lesser amounts in yeast, roots of higher plants and animal tissue.[28]

Adenosine thiamine diphosphate

Adenosine thiamine diphosphate (AThDP) or thiaminylated adenosine diphosphate exists in small amounts in vertebrate liver, but its role remains unknown.[28]

History

Thiamine was the first of the water-soluble vitamins to be described,[27] leading to the discovery of more such trace compounds essential for survival and to the notion of vitamin.

In 1884, Kanehiro Takaki (1849–1920), a surgeon general in the Japanese navy, rejected the previous germ theory for beriberi and hypothesized that the disease was due to insufficiencies in the diet instead.[29]Switching diet on a navy ship, he discovered that substituting a diet of white rice only, with one also containing barley, meat, milk, bread, and vegetables nearly eliminated beriberi on a 9-month sea voyage. However, Takaki had added many foods to the successful diet and he incorrectly attributed the benefit to increased nitrogen intake, as vitamins were unknown substances at the time. Nor was the Navy convinced of the need for so expensive a program of dietary improvement, and many men continued to die of beriberi, even during the Russo-Japanese war of 1904–5. Not until 1905, after the anti-beriberi factor had been discovered in rice bran (removed by polishing into white rice) and in brown barley rice, was Takaki's experiment rewarded by making him a baron in the Japanese peerage system, after which he was affectionately called "Barley Baron".
The specific connection to grain was made in 1897 by 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.[30] He attributed beriberi to a nerve poison in the endosperm of rice, from which the outer layers of the grain gave protection to the body. An associate, Gerrit Grijns (1865–1944), correctly interpreted the connection between excessive consumption of polished rice and beriberi in 1901: He concluded that rice contains an essential nutrient in the outer layers of the grain that is removed by polishing.[31]

Eijkman was eventually awarded the Nobel Prize in Physiology and Medicine in 1929, because his observations led to the discovery of vitamins. These compounds were named by Polish biochemist Casimir Funk. In 1911, Casimir Funk isolated the antineuritic substance from rice bran that he called a "vitamine" (on account of its containing an amino group). Dutch chemists, Barend Coenraad Petrus Jansen (1884–1962) and his closest collaborator Willem Frederik Donath (1889–1957), went on to isolate and crystallize the active agent in 1926,[32] whose structure was determined by Robert Runnels Williams (1886–1965), a US chemist, in 1934. Thiamine ("sulfur-containing vitamin") was synthesized in 1936 by the same group.[33]

Thiamine was first named "aneurin" (for anti-neuritic vitamin).[34] 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. If not treated, the animal will die after a few days. Administration of thiamine at the stage of opithotonos will lead to a complete cure of the animal within 30 min. As no morphological modifications were observed in the brain of the pigeons before and after treatment with thiamine, Peeters introduced the concept of biochemical lesion.[35]

When Lohman and Schuster (1937) showed that the diphosphorylated thiamine derivative (thiamine diphosphate, ThDP) was a cofactor required for the oxydative decarboxylation of pyruvate,[36] (a reaction now known to be catalyzed by pyruvate dehydrogenase), the mechanism of action of thiamine in the cellular metabolism seemed to be elucidated. At present, 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.

Finally, the mechanism by which the thiamine moiety of ThDP exerts its coenzyme function by proton substitution on position 2 of the thiazoliiumring was elucidated by Ronald Breslow in 1958.[37]