

Introduction

Pantothenic acid was discovered in 1933 and belongs to the group of water-soluble B vitamins. Its name originates from the Greek word “pantos”, meaning “everywhere”, as it can be found throughout all living cells.

Functions

Pantothenic acid, as a constituent of coenzyme A (a coenzyme of acetylation), plays a key role in the metabolism of carbohydrates, proteins and fats, and is therefore important for the maintenance and repair of all cells and tissues. Coenzyme A is involved in reactions that supply energy, in the synthesis of essential lipids (e.g. sphingolipids, phospholipids), sterols (e.g. cholesterol), hormones (e.g. growth, stress and sex hormones), neurotransmitters (e.g. acetylcholine), porphyrin (a component of haemoglobin, the oxygen-carrying red blood cell pigment) and antibodies, and in the metabolism of drugs (e.g. sulphonamides) and in alcohol detoxification. Another essential role of pantothenic acid concerns acyl carrier protein, an enzyme involved in the synthesis of fatty acids. In the process of fat burning, pantothenic acid works in concert with coenzyme Q10 and L-carnitine.

Main functions in a nutshell:

- Metabolism of carbohydrates, proteins and fats
- Supply of energy from foods
- Synthesis of essential lipids, sterols, hormones, neurotransmitters, and porphyrin
- Metabolism of drugs and alcohol detoxification

Dietary sources

The active vitamin is present in virtually all plant, animal and microbial cells. Thus pantothenic acid is widely distributed in foods, mostly incorporated into coenzyme A. Its richest sources are yeast and organ meats (liver, kidney, heart, brain), but eggs, milk, vegetables, legumes and whole-grain cereals are more common sources.

Pantothenic acid is synthesised by intestinal micro-organisms, but the extent and significance of this enteral synthesis is unknown.

Pantothenic acid content of foods

Food	Pantothenic acid (mg/100g)
Veal liver	7.9
Brewer's yeast	7.2
Peanuts	2.1
White mushrooms	2.1
Egg	1.6
Wheat germ	1
Herring	0.94
Milk	0.35
Vegetables	0.2-0.6

(Souci, Fachmann, Kraut)

Absorption and body stores

Most of the pantothenic acid in food exists in the form of coenzyme A, and pantothenic acid is released by a series of enzyme reactions in the small intestine. It is then absorbed by passive diffusion into the portal circulation and transported to the tissues, where re-synthesis of the coenzyme occurs. About half of the pantothenic acid in the diet is actually absorbed. If calcium pantothenate or pan-

tothenic acid are ingested as nutritional supplements, they must first be converted to pantetheine by intestinal enzymes before being absorbed. Topical and orally applied D-pantethenol (the alcoholic form of pantothenic acid that can, e.g., be found in many cosmetic products) is also absorbed by passive diffusion and transformed to pantothenic acid by enzymatic oxidation. The highest concentrations in the body are in the liver, adrenal glands, kidneys, brain, heart and testes. Total pantothenic acid levels in whole blood are at least 1 mg/L in healthy adults; most of it exists as coenzyme in the red blood cells. Urinary excretion in the form of pantothenic acid generally correlates with dietary intake, but variation is large (2-7 mg daily). During lactation, a large proportion of the intake reaches the milk (1-5 mg daily).

Measurement

Due to the fact that dietary deficiency is practically unknown, little research has been conducted through assays to assess pantothenate status in man. Nutritional status can be deduced from amounts of pantothenate excreted in urine. Less than 1 mg daily is considered abnormally low. A more convenient approach is determination of pantothenate in serum, or preferably whole blood, by microbiological methods. Although these assays are highly sensitive and specific, they are slow and tedious to perform. New methods, such as HPLC/MS (High Performance Liquid Chromatography / mass spectrometry) and immunologic methods, have also been applied. Another method suggested for assessing nutritional status is the sulphanilamide acetylation test, which measures the activity of coenzyme A in the blood. Whole blood levels typically range from 0.9 – 1.5 µmol/L.

Stability

Pantothenic acid is stable under neutral conditions, but is readily destroyed by heat in alkaline or acid solutions. Up to 50% may be lost during cooking (due to leaching) and up to 80% as a result of food processing and refining (canning, freezing, milling etc.). Pasteurisation of milk only causes minor losses.

Interactions

Positive interactions

Various studies have indicated that vitamin B₁₂ may aid in the conversion of free pantothenic acid into coenzyme A. In the absence of B₁₂, coenzyme A production is decreased and fat metabolism impaired. In animal experiments, ascorbic acid (vitamin C) was shown to lessen the severity of symptoms due to pantothenic acid deficiency; vitamin A, vitamin B₆, folic acid and biotin are also necessary for proper utilisation of pantothenic acid.

Negative interactions

Ethanol causes a decrease in the amount of pantothenic acid in tissues, with a resulting increase in serum levels. It has therefore been suggested that pantothenic acid utilisation is impaired in alcoholics. Birth control pills containing estrogen and progestin may increase the requirement for pantothenic acid. The most common antagonist of pantothenic acid used experimentally to accelerate the appearance of deficiency symptoms is omega-methyl pantothenic acid. L-pantothenic acid has also been shown to have an antagonistic effect in animal studies. Methyl bromide, a fumigant used to control vermin in places where food is stored, destroys the pantothenic acid in foods exposed to it.

Deficiency

Since pantothenic acid occurs to some extent in all foods, it is generally assumed that dietary deficiency of this vitamin is extremely rare. However, pantothenic acid deficiency in humans is not well documented and probably does not occur in isolation but in conjunction with deficiencies of other B vitamins. Clinical manifestations that can be clearly ascribed to dietary deficiency of pantothenic acid have not been identified, although it has been implicated in "burning feet" syndrome, a condition observed among malnourished prisoners of war in the 1940s. Deficiency symptoms have been produced experimentally by administering the antagonist omega-methyl pantothenic acid. They include fatigue, headaches, insomnia, nausea, abdominal cramps, vomiting and flatulence. The subjects complained of tingling sensations in the arms and legs, muscle cramps and impaired coordination. There was cardiovascular instability and impaired responses to insulin, histamine and ACTH (a stress hormone).

Homopantothenate is a pantothenic acid antagonist that has been used in Japan to enhance mental function, especially in Alzheimer's disease. A rare side effect was an abnormal brain function resulting from the failure of the liver to eliminate toxins (hepatic encephalopathy). This condition was reversed by pantothenic acid supplementation, suggesting it was due to pantothenic acid deficiency caused by the antagonist. In experiments with mice it has been shown that a deficiency of pantothenic acid leads to skin irritation and greying of the fur, which were reversed by giving pantothenic acid. Pantothenic acid has since been added to shampoo, although it has never been successful in restoring hair colour in humans.

Groups at risk of deficiency

- Alcoholics
- Women on oral contraceptives
- People with insufficient food intake (e.g. elderly, post-operative)
- People with impaired absorption (due to certain intestinal diseases)

Current recommendations in the USA

RDA*

Infants	< 6 months	1.7mg (AI)
Infants	7-12 months	1.8mg (AI)
Children	1-3 years	2mg (AI)
Children	4-8 years	3mg (AI)
Children	9-13 years	4mg (AI)
Adults	>14 years	5mg (AI)
Pregnancy		6mg (AI)
Lactation		7mg (AI)

*The Dietary Reference Intakes (DRIs) are actually a set of four reference values: Estimated Average Requirements (EAR), Recommended Dietary Allowances (RDA), Adequate Intakes (AI), and Tolerable Upper Intake Levels, (UL) that have replaced the 1989 Recommended Dietary

Allowances (RDAs). The RDA was established as a nutritional norm for planning and assessing dietary intake, and represents intake levels of essential nutrients considered to meet adequately the known needs of practically all healthy people

Disease prevention and therapeutic use

Although isolated deficiency states are rarely observed, various investigators have noted changes in pantothenic acid levels in various diseases, and pharmacological amounts of the vitamin are used in the treatment of numerous conditions. In most cases, however, the claimed therapeutic responses have not been confirmed by controlled studies in humans.

For the treatment of deficiency due to impaired absorption, intravenous or intramuscular injections of 500 mg several times a week are recommended. Postoperative ileus (paralysis of the intestine) requires doses of up to 1000 mg every six hours.

Panthenol is applied topically to skin and mucosa to speed healing of wounds, ulcers and inflammation, such as cuts and grazes, burns, sunburn, nappy rash, bed sores, laryngitis and bronchitis. In combination, pantothenic acid and ascorbic acid significantly enhance post surgical therapy and wound healing. The healing process of conjunctiva and the cornea after reconstructive surgery of the epithelium has also been accelerated. Pantothenic acid has been tried, with varying results, to treat various liver conditions, arthritis, and constipation in the elderly; to prevent urinary retention after surgery or childbirth; and (together with biotin) to prevent baldness. It has also been reported to have a protective effect against radiation sickness.

Pantethine is used to normalise lipid profiles, as it lowers elevated triglycerides and LDL cholesterol while raising levels of the beneficial HDL cholesterol. Pantethine actually consists of two molecules of pantetheine joined by two molecules of sulphur (a disulphide bridge). It is especially effective at lowering elevated blood lipids in patients with diabetes without hindering blood sugar control.

Recommended Dietary Allowance (RDA)

It is widely agreed that there is insufficient information available on which to base an RDA for pantothenic acid. Most countries that make recommendations therefore give an estimate of safe and adequate levels for daily intake. These adequate intake levels (AI) are based on estimated dietary intakes in healthy population groups and range, depending on the health authority concerned, from 2 to 14 mg for adults.

Safety

Pantothenic acid is essentially considered to be nontoxic, and no cases of hypervitaminosis have ever been reported. As much as 10 g daily in humans produces only minor gastrointestinal disturbance (diarrhoea). Due to the lack of reports of adverse effects the main regulatory authorities have not defined a tolerable upper level of intake (UL) for pantothenic acid.

Supplements, food fortification and cosmetics

Pure pantothenic acid is a viscous hygroscopic oil that is chemically not very stable. Supplements therefore usually contain the calcium salt, or alcohol, panthenol. Both are highly water soluble and are rapidly converted to free acid in the body. Calcium pantothenate is often included in multivitamin preparations; panthenol is the more common form used in mono-preparations, which are available in a wide variety of pharmaceutical forms (e.g. solutions for injection and local

application, aerosols, tablets, ointments and creams). Pantethine, a derivative of pantothenic acid, is used as a cholesterol and triglyceride-lowering drug in Europe and Japan and is available in the U.S. as a dietary supplement.

Pantothenate is added to a variety of foods, the most important of which are breakfast cereals and beverages, dietetic and baby foods.

D-Panthenol is often used in cosmetic products. In skin care products, it helps to keep the skin moist and supple, stimulates cell growth and tissue repair, and inhibits inflammation and reddening. As a moisturiser and conditioner in hair care products, it protects against and repairs damage due to chemical and mechanical procedures (brushing, combing, shampooing, perming, colouring etc.), and imparts sheen and luster.

Industrial production

Pantothenic acid is chemically synthesised by condensation of D-pantolactone with P-alanine. Addition of a calcium salt produces colourless crystals of calcium pantothenate. Panthenol is produced as a clear, almost colourless, viscous hygroscopic liquid.



History

- 1931** Williams and Truesdail separate an acid fraction from “bios”, the growth factor for yeast discovered in 1901 by Wildiers.
- 1933** Williams and coworkers show this fraction to be a single acid substance essential for the growth of yeast. Because they find it in a wide range of biological materials, they suggested calling it “pantothenic acid”.
- 1938** Williams and associates establish the structure of pantothenic acid
- 1939** Jukes and colleagues show the similarity between pantothenic acid and the chick antidermatitis factor.
- 1940** Total synthesis of the vitamin is achieved independently by Williams and Major, Stiller and associates, Reichstein and Grüssner, and Kuhn and Wieland.
- 1947** Lipmann and his associates identify pantothenic acid as one of the components of the coenzyme they had discovered in liver two years earlier.
- 1953** The full structure of coenzyme A is elucidated by Baddiley and colleagues. Lipmann receives the Nobel Prize, together with Krebs, for his work on coenzyme A and its role in metabolism.
- 1954** Bean and Hodges report that pantothenic acid is essential in human nutrition. Subsequently, they and their colleagues conduct several further studies to produce deficiency symptoms in healthy humans using the antagonist omega-methyl pantothenic acid.
- 1965** Pugh and Wakil identify the acyl carrier protein as an additional active form of pantothenic acid.
- 1976** Fry and her associates measure the metabolic response of humans to deprivation of pantothenic acid without involvement of an antagonist.



Roger John Williams



Fritz Albert Lipmann



Tadeusz Reichstein