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Pantothenic Acid

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History

The discovery of pantothenic acid followed the same path that led to the discovery of other water-soluble vitamins: studies utilizing bacteria and single-cell eukaryotic organisms (e.g., yeast), animal models, and thoughtful chemical analysis. It was largely the efforts of research groups associated with R.J. Williams, C.A. Elvehjem, and T.H. Jukes that resulted in the identification of pantothenic acid as an essential dietary factor. Williams et al.[1] established that pantothenic acid was required for the growth of certain bacteria and yeast. Next, Elvehjem et al.[2] and Jukes et al.[3,4] demonstrated that pantothenic acid was a growth and "anti-dermatitis" factor for chickens. Williams coined the name "pantothenic" acid from the Greek meaning "from everywhere" to indicate its widespread occurrence in foodstuffs.[1,5] The eventual characterization of pantothenic acid by Williams took advantage of observations that the anti-dermatitis factor present in acid extracts of various food sources (pantothenic acid) did not bind to fuller's earth under acidic conditions. Using chromatographic and fractionation procedures that were typical of the 1930s (solvent-dependent chemical partitioning), Williams isolated several grams of pantothenic acid for structural determination from 250 kg of liver.[5] With this information, a number of research groups contributed to the chemical synthesis and commercial preparation of pantothenic acid.

In the 1950s, one of the functional forms of pantothenic acid, coenzyme A (CoA), was discovered as the cofactor essential for the acetylation of sulfonamides and choline.[6] In the mid-1960s, pantothenic acid was next identified as a component of acyl carrier protein (ACP) in the fatty acid synthesis complex.[7] These developments, in addition to a steady series of observations throughout this period on the effects of pantothenic acid deficiency in humans and other animals, provided the foundation for our current understanding of this vitamin.

Chemistry and Nomenclature

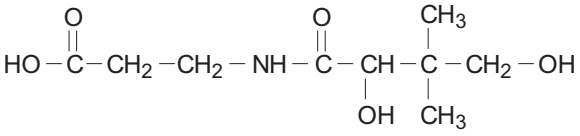
The chemical structure of pantothenic acid consists of pantoic acid and β-alanine bound in amide linkage (Figure 1a). Metabolic processing of pantothenic acid, described in detail below, produces the important intermediate, 4′-phosphopantetheine (Figure 1b), which includes β-mercaptoethylamine (cysteamine) bound in amide linkage to the terminal carboxyl group of the molecule. 4′-Phosphopantetheine serves as a covalently linked prosthetic group for ACP (Figure 1c). Further metabolic processing with the addition of adenine and ribose 3′-phosphate produces the essential cofactor, CoA (Figure 1d).

Pure pantothenic acid is a water-soluble, viscous, yellow oil. It is stable at neutral pH, but is readily destroyed by acid, alkali, and heat. Calcium pantothenate, a white, odorless, crystalline substance, is the form of pantothenic acid usually found in commercial vitamin supplements due to its greater stability than the pure acid.[8] Early literature referred to pantothenic acid as chick anti-dermatitis factor, filtrate factor, and vitamin B_3. Today, it is often referred to as vitamin B_5, although the origin of this designation is obscure.

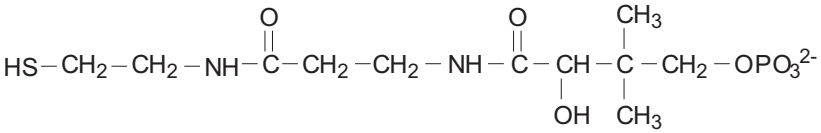
Intestinal Absorption, Plasma Transport, and Excretion

The vast majority of pantothenic acid in food is present as a component of CoA or 4′-phosphopantetheine. To be absorbed, these substances must first be hydrolyzed.[9] This occurs in the intestinal lumen by the sequential activity of two hydrolases, pyrophosphatase and phosphatase, with pantetheine as the product. Pantetheine is either absorbed as is, or is further metabolized to pantothenic acid by a third intestinal hydrolase, pantetheinase.

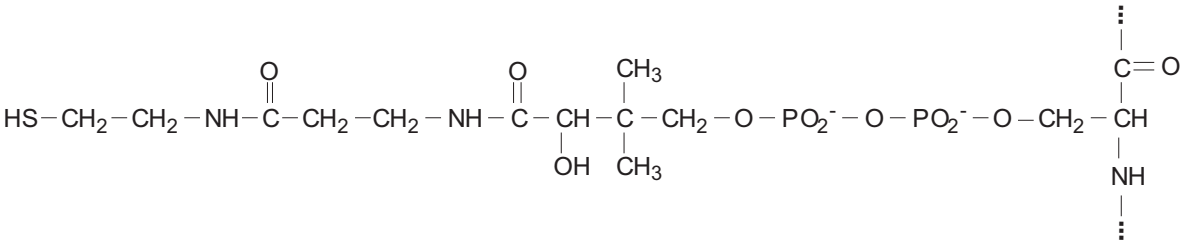
A. Pantothenic Acid



B. 4'-Phosphopantetheine



C. Acyl Carrier Protein



D. Coenzyme A

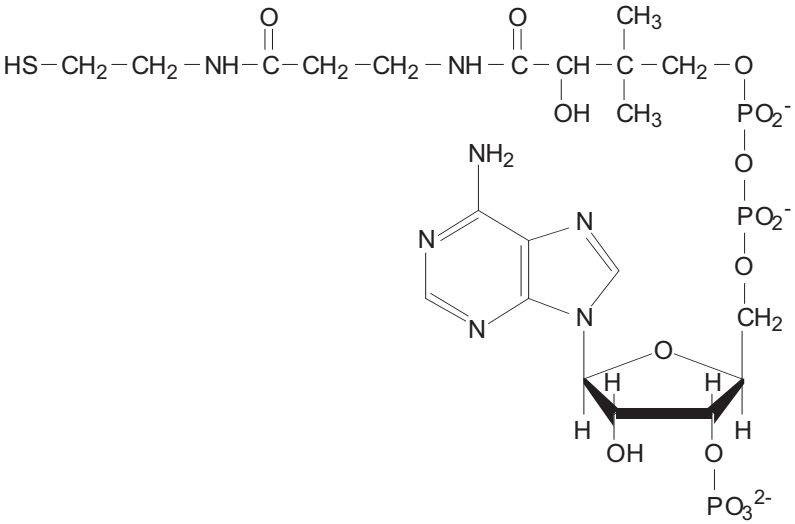


Figure 1. Chemical structures of pantothenic acid, 4′-phosphopantetheine, acyl carrier protein, and coenzyme A.

In rats, pantothenic acid absorption was initially found to occur in all sections of the small intestine by simple diffusion.[9] However, subsequent work in rats and chicks indicated that at low concentrations, the vitamin is absorbed by a saturable, sodium-dependent transport mechanism.[10] Moreover, it has been demonstrated that pantothenic acid shares a common membrane transport system in the small intestine with another vitamin, biotin. In vitro experiments utilizing Caco-2 cell mono-layers as a model of intestinal absorption established that pantothenic acid uptake is inhibited competitively by biotin and vice versa.[11] Similar observations have been made in transport experiments involving the blood-brain barrier,[12] heart,[13] and placenta.[14] After absorption, pantothenic acid enters the circulation, where it is taken up by cells in a manner similar to that of intestinal absorption (see below). The vitamin is excreted in the urine primarily as pantothenic acid. This occurs after its release from CoA by a series of hydrolysis reactions that cleave off the phosphate and β-mercaptoethylamine moieties.

Functions and Cellular Regulation

Coenzyme A and Acyl Carrier Protein Synthesis

Pantothenic acid is nutritionally essential due to the inability of animal cells to synthesize the pantoic acid moiety of the vitamin. The primary function of pantothenic acid is to serve as substrate for the synthesis of CoA and ACP (Figure 2). The first step is the phosphorylation of pantothenic acid to 4′-phosphopantothenic acid by pantothenic acid kinase.[15,16] The kinase possesses a broad pH optimum (between 6 and 9) with a K_m for pantothenic acid of about 20 μM. Mg-ATP is used as the nucleotide substrate for this phosphorylation reaction with a K_m of about 0.6 mM.

The pantothenic acid kinase reaction also serves as the primary control point in the synthesis of CoA and ACP. The reaction is activated and inhibited nonspecifically by various anions. More significantly, feedback inhibition of the kinase by CoA or CoA derivatives governs flux

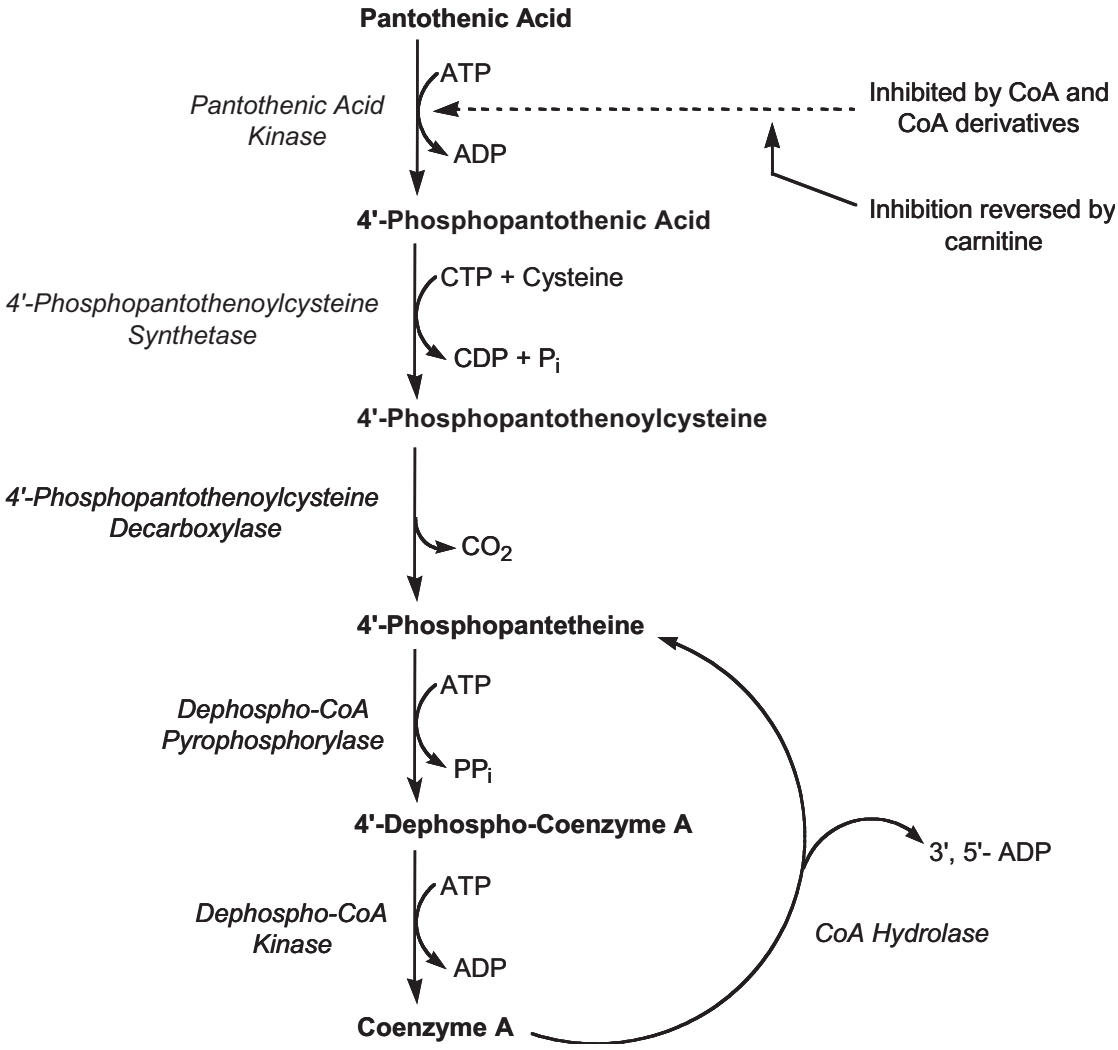


Figure 2. Metabolic conversion of pantothenic acid to coenzyme A.

through the subsequent steps in the CoA synthesis pathway and defines the upper threshold for intracellular CoA cofactor levels. Inhibition by acetyl-CoA is slightly greater than that of free CoA. The inhibition by free CoA is uncompetitive with respect to pantothenate concentration, with a K_i for inhibition of 0.2 μM.

L-carnitine, which is important for the transport of fatty acids into mitochondria, is a nonessential activator of pantothenic acid kinase. Carnitine has no effect by itself, but specifically reverses the inhibition by CoA. In heart tissue, the free carnitine content varies directly with the phosphorylation of pantothenic acid. Thus, these properties of the kinase provide a potential mechanism for the control of CoA synthesis and the regulation of cellular pantothenic acid content: feedback inhibition by CoA and its acyl esters that is reversed by changes in the concentration of free carnitine. However, it is important to underscore that the free concentration of acyl CoA in cells is low and variable, because the bulk of acyl derivatives are protein bound. Moreover, similar to CoA, carnitine exists in both free and acylated forms, and reversal of kinase inhibition by CoA does not occur when carnitine is acylated.[15] The ratio of free to acylated carnitine varies considerably depending on feeding and hormonal influences, with insulin being particularly important. Fasting and diabetes (states of low insulin) increase pantothenic acid kinase activity and the total content of CoA.[17-19] In addition, the perfusion of heart preparations or incubation of liver cells with glucose, pyruvate, or palmitate markedly inhibits pantothenic acid phosphorylation, due to reduction in free carnitine and increases in the free and acylated forms of CoA.

Following 4′-phosphopantothenic acid formation, the subsequent steps in CoA synthesis are carried out on a protein complex (approximately 400,000 Da) with multifunctional catalytic sites. Important enzymatic features of this complex include dephospho-CoA-pyrophosphorylase activity, which catalyzes the reaction between 4′-phosphopantetheine and ATP to form 4′-dephospho-CoA; dephospho-CoA-kinase activity, which catalyzes the ATP-dependent final step in CoA synthesis; and CoA hydrolase activity, which catalyzes the hydrolysis of CoA to 3′,5′-ADP and 4′-phosphopantetheine. This sequence of reactions is referred to as the CoA/4′-phosphopantetheine cycle, and it provides a mechanism by which the 4′-phosphopantetheine can be recycled to form CoA. Each turn of the cycle utilizes two molecules of ATP and produces one molecule of ADP, one molecule of pyrophosphate, and one molecule of 3′,5′-ADP (Figure 2).[20]

ACP is sometimes referred to as a "macro-cofactor," because in bacteria, yeast, and plants, it is composed of a polypeptide chain (mol. wt of approximately 8500–8700 Da) to which 4′-phosphopantetheine is attached. However, in higher animals, ACP is most often associated with a fatty acid synthase complex that is composed of two very large protein subunits (mol. wt. about 250,000 Da each). The carrier segment or domain of the fatty acid synthetic complex is also called the ACP, one of seven functional or catalytic domains on each of the two subunits that comprise fatty acid synthase. The inactive ACP apopolypeptide (or domain) is converted to an active holoform (or domain) by the post-translational transfer of a 4′-phosphopantetheinyl moiety to the side-chain hydroxyl of a serine residue at the active center of ACP. The reaction is catalyzed by 4′-phosphopantetheinyl transferase, which uses CoA as the 4′-phosphopantetheine substrate. Although there are few data related to the regulation of holo-ACP peptide or domain formation, the 4′-phosphopantetheine transferase gene recently has been cloned from a human source.[21]

Selected Functions of CoA and ACP

Important functions of CoA and ACP are listed in Table 1. Principally, CoA is involved in acetyl and acyl transfer reactions and processes related to oxidative metabolism and catabolism, whereas ACP is involved pri-

Table 1. Selected Functions of Coenzyme A (CoA) and Acyl Carrier Protein (ACP)

Function	Importance
Carbohydrate-Related	Oxidative metabolism
Citric acid cycle transfer reactions	Production of carbohydrates important to cell structure
Acetylation of sugars (e.g. N-acetylglucosamine)	
Lipid-Related	
Phospholipid biosynthesis	Cell membrane formation and structure
Isoprenoid biosynthesis	Cholesterol and bile salt production
Steroid biosynthesis	Steroid hormone production
Fatty acid elongation, acyl (fatty acid) and triacyl glyceride synthesis	Ability to modify cell membrane fluidity Energy storage
Protein-related	
Protein acetylation	Altered protein conformation; activation of certain hormones and enzymes (e.g., adrenocoriticotropin); transcription (e.g., acetylation of histone)
Protein acylation (myristic and palmitic acid additions) and prenylation	Compartmentalization and activation of hormones and transcription factors

marily in synthetic reactions. The adenosyl moiety of CoA provides a site for tight binding to CoA-requiring enzymes, while allowing the phosphopantetheine portion to serve as a flexible arm to move substrates from one catalytic center to another. Similarly, when pantothenic acid (as 4′-phosphopantetheine) in ACP is used in the transfer reactions associated with the fatty acid synthase process, 4′-phosphopantetheine also functions as a flexible arm that allows for an orderly and systematic presentation of acyl derivatives to each of the active centers of the fatty acid synthase complex. A summary of catalytic sites and their functions in the fatty acid synthase complex is presented in Table 2.

In addition to fatty acid synthesis, hints that ACP-like factors may perform other functions in humans and animals come from observations that an oligosaccharide-linked ACP acts as a transmethylation inhibitor in porcine liver.[22] ACP is also structurally homologous to acidic ribosomal structural proteins, such as ribosomal protein P2.[23] Moreover, in bacteria and plants, ACP is important in a number of pathways, such as amino acid synthesis and the formation of polyketides, a remarkably diverse group of secondary metabolites that include antibiotics such as erythromycin, cholesterol-lowering drugs such as lovastatin, and putative anti-aging compounds such as resveratrol.[24]

It is also important to appreciate that intermediates arising from the transfer reactions catalyzed by CoA and 4′-phosphopantetheine in ACP may be viewed as "high-energy" compounds. CoA or ACP reacts with acetyl or acyl groups to form thioesters. Thioesters (—S—CO—R) are thermodynamically less stable than typical esters (—O—CO—R) or amides (—N—CO—R). The double-bond character of the C—O bond in —S—CO—R does not extend significantly into the C—S bond. This causes thioesters to have relatively a high energy potential, and for most reactions involving CoA or ACP, no additional energy (e.g., from ATP hydrolysis) is required for transfer of the acetyl or acyl group. For example, at pH 7.0, the $-\Delta G$ of hydrolysis is about 7.5 kcal for acetyl-CoA and 10.5 kcal for acetoacetyl-CoA compared with 7 to 8 kcal for the hydrolysis of ATP to AMP and pyrophosphate or ADP and phosphate. The terminal thiol group of CoA and ACP is also ideally suited for nucleophilic substitution reactions involving activated carboxylic acids and α- and β-carbonyl functions.[25]

Cellular Regulation of Pantothenic Acid and CoA Levels

As noted above, both biotin and pantothenic acid appear to share the same transporters for cellular uptake and

Table 2. Catalytic Sites Associated with the Fatty Acid Synthase Complex

Step	Action(s)
1. Acetyl transferase	Catalyzes the transfer of an activated acetyl group on CoA to the sulfidryl group of 4′-phosphopantetheine (ACP domain); in a subsequent step, the acetyl group is transferred to a second cysteine-derived sulfidryl group near active site of 3-oxoacyl synthase (see step 3) leaving the 4′-phosphopantetheine sulfidryl group free for Step 2
2. Malonyl transferase	This enzyme catalyzes the transfer of successive in-coming malonyl groups to 4′-phosphopantetheine
3. 3-Oxoacyl synthetase	The first condensation reaction in the process, catalyzed by 3-oxoacyl synthase, in which attack on malonyl-ACP by the acetyl moiety (transferred in Step 1) occurs with decarboxylation and condensation to yield a 3-oxobutryl (acetoacetyl) derivative; in the second through the seventh cycles, it is the newly formed acyl moieties that attacks the malonyl group added at each cycle (see Step 6)
4. Oxoacyl reductase	Reductions of acetoacetyl or 3 oxoacyl intermediates involve NADPH; the first cycle of this reaction generates D-hydroxybutyrate, and in subsequent cycles, hydroxyfatty acids
5. 3-Hydroxyacyl dehydratase	This enzyme catalyzes the removal of a molecule of water from the 3-hydroxyacyl derivatives produced in Step 4 to form enoyl derivatives
6. Enoyl reductase	Reduction of the enoyl derivatives (Step 5) by a second molecule of NADPH generates a fatty acid; this acyl group is also transferred to the sulfidryl group adjacent to 3-oxoacyl synthase, as described in step 1, until a 16-carbon paimitoyl group is formed; this group, still attached to the 4′-phosphopantetheine arm, is highly specific substrate for the remaining enzyme of the complex, thioester hydrolase
7. Thioester hydrolase	This enzyme liberates palmitic acid (Step 6) from the 4′-phosphopantetheine arm

ACP = acyl carrier protein; CoA = coenzyme A.

perhaps efflux.[11] Whether it is an intestinal, hepatic, or cardiac muscle cell, the process for pantothenic acid cellular uptake appears saturable, with an apparent K_m of 15 to 20 μM. Transport across cell membranes appears to occur by carrier-mediated, sodium gradient-dependent, and electroneutral mechanisms.[13,26-29] Pantothenic acid cellular uptake has also been linked to protein kinase C and calmodulin-dependent regulatory and signaling pathways.[27] The dependence on protein kinase C is based on observations that pretreatment of cells with a protein kinase C activator such as phorbol 12-myristate 13-acetate or 1,2-dioctanoyl-glycerol significantly inhibits pantothenic acid uptake. If an inward sodium gradient is imposed, a rapid uptake of pantothenic acid is observed. Uptake of pantothenic acid is reduced when sodium is replaced by potassium or if external sodium is reduced below 40 mM. Ouabain, gramicidin D, cyanide, azide, and 2,4-dinitrophenol also act as inhibitors.

With regard to efflux, unlike uptake, the export of pantothenic acid is unaffected by the addition of pantothenic acid, sodium, ouabain, gramicidin D, or 2,4-dinitrophenol to the external medium. Moreover, the metabolic state also has an impact on uptake. For example, in the perfused heart, pantothenic acid transport is significantly increased when hearts are perfused and are acting as "working" hearts because of addition of a fuel source.[27]

That active uptake of pantothenic acid is underscored by the differences in cellular versus plasma concentrations of free pantothenic acid. The cellular concentration of free pantothenic acid in the liver is 10 to 15 μM and in the heart about 100 μM, compared with 1 to 5 μM observed in plasma. Similarly, the unidirectional influx of pantothenic acid across cerebral capillaries (the blood-brain barrier) occurs by a low-capacity, saturable transport system with a half-saturation concentration approximately 10 times the plasma pantothenic acid concentration.[30,31] For comparison, the concentrations of CoA and ACP are 50 to 100 μM and 10 μM, respectively, in the cytosol of typical cells. In mitochondria, the CoA concentration can be as much as 10- to 20-fold higher, or 70% to 90% of the total cellular CoA content.

In addition to cellular transport, enzymes associated with CoA synthesis also have significant impact on maintaining cellular levels of pantothenic acid and related compounds. As described above, the most important of these enzymes is pantothenic acid kinase.[15]

Dietary Sources and Requirements

Pantothenic acid is found in a wide variety of foods of both plant and animal origin at levels ranging from 20 to 50 μg/g. Particularly rich sources of pantothenic acid include chicken, beef, liver and other organ meats, whole grains, potatoes, and tomato products.[32] Royal bee jelly and ovaries of tuna and cod also have high levels of the vitamin.[33] Because of its thermal lability and susceptibility to oxidation, significant amounts of pantothenic acid are lost from highly processed foods, including refined grains and cooked or canned meats and vegetables. Processing and refining whole grains results in a 37% to 47% loss of pantothenic acid, while canning of meats, fish, and dairy products leads to losses of 20% to 35%.[34] Greater losses of the vitamin occur during canning (46%–78%) and freezing (37%–57%) of vegetables. Pantothenic acid is also synthesized by intestinal microorganisms,[35] although the amount produced and the availability of the vitamin from this source is unknown.

The primary source of pantothenic acid in food is CoA. Intestinal phosphatases and nucleosidases are capable of very efficient hydrolysis of CoA so that near-quantitative release of pantothenic acid occurs as a normal part of digestion. Further, the overall K_m for pantothenic acid intestinal uptake is 10 to 20 μM. At an intake of about 10 to 15 mg of CoA, the amount of CoA in a typical meal, the pantothenic acid concentration in luminal fluid would be about 1 to 2 μM. At this concentration, pantothenic acid would not saturate the transport system, and as a consequence, should be efficiently and actively absorbed.[11]

A dietary reference intake has yet to be established for pantothenic acid. Adequate intakes (AIs) for men and women throughout the life cycle have been suggested based on observed mean intakes and estimates of basal excretion in urine (Table 3).[36] Urinary excretion of pantothenic acid only exceeds basal levels when intakes are

Table 3. Adequate Intakes (AIs) for Pantothenic Acid (From Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington, DC: National Academies Press; 1998. Available online at: http://www.nap.edu/openbook/0309065542/html/)

Age Group	AI *(mg/d)*
Infants	
0–5 months	1.7
6–12 months	1.8
Children	
1–3 years	2.0
4–8 years	3.0
9–13 years	4.0
Adolescents	
14–18 years	5.0
Adults	
19–50 years	5.0
> 50 years	5.0
Pregnant women	6.0
Lactating women	7.0

greater than 4 mg/d in young adult males. Thus, an intake of 4 mg/d likely reflects the level at which saturation of the body pool occurs.[37] Estimates of dietary intake in healthy adults have ranged from 4 to 7 mg/d.[37-40] There is no evidence to suggest that this range of intake is inadequate, and 5 mg/d has been set as the AI for adults. For those older than 51 years, the AI remains the same, as there is currently no basis for expecting an increased requirement in elderly individuals. During pregnancy, the AI is increased to 6 mg/d based on usual intakes of 5.3 mg/d[41] with rounding up. During lactation, the AI is increased further to 7 mg/d, accounting for additional secretion of the vitamin in human milk (1.7 mg/d) and the lower maternal blood concentrations reported when intakes are about 5 to 6 mg/d.[41-43] This is likely the result of efficient sequestering of the vitamin in human milk, estimated to be 0.4 mg for every 1 mg of pantothenic acid consumed during active lactation.[44]

The AI for infants reflects the mean intake of infants fed principally with human milk, which contains about 5 to 6 mg of pantothenic acid per 1000 kcal. Values for children and adolescents have largely been extrapolated from adult values. These values are supported by studies comparing intake and urinary excretion of the vitamin in preschool children.[45] Dietary intake of pantothenic acid was 3.8 and 5 mg/d in children of high and low socioeconomic status, respectively, and urinary excretion was 3.36 and 1.74 mg/d, respectively. In a separate study, 35 healthy girls 7 to 9 years of age were fed defined diets and urinary excretion was measured.[46] The average daily excretion was 1.3 mg/d when intake was 2.79 mg/d, and 2.7 mg/d when intake was 4.45 mg/d. Therefore, intakes of 2.8 to 4.5 mg/d exceed urinary excretion of the vitamin. In healthy adolescents (13–19 years of age), 4-day diet records indicated that the average pantothenic acid intake was 6.3 mg/d for males and 4.1 mg/d for females.[47] The average urinary excretion in this latter study was 3.3 and 4.5 mg/d for males and females, respectively, while whole blood pantothenic acid concentrations averaged 1.86 μmol/L and 1.57 μmol/L, respectively. Normal blood concentrations of the vitamin in healthy individuals have been reported to range from 1.6 to 2.7 μmol/L.[48] Taken together, these data indicate that intakes of 4 mg/d is sufficient to maintain normal blood concentrations in adolescents.

Using the estimate of 20 to 50 μg pantothenic acid per gram typically found in edible animal and plant tissues, it is possible to meet the AI for adults with a mixed diet containing as little as 100 to 200 g of solid food, the equivalent of a mixed diet corresponding to 600 to 1200 kcal or 2.4 to 4.8 MJ. The typical Western diet contains 6 mg or more of available pantothenic acid.[37] For a more detailed review of the AIs for pantothenic acid, see the Dietary Reference Intakes report from the Institute of Medicine.[36]

Deficiency and Toxicity

The essentiality of pantothenic acid has been documented in a wide variety of animal species. The classical signs of deficiency, first recognized by Elvehjem, Jukes, and colleagues[4-6] in chickens, include growth retardation and dermatitis. Many other physiological systems are affected by pantothenic acid deficiency, owing to the diversity of metabolic functions in which CoA and ACP participate. Neurological, immunological, hematological, reproductive, and gastrointestinal pathologies have been reported. The effects of pantothenic acid deficiency in different species are summarized in Table 4.[49-63]

Assuming that the human adult requirement for pantothenic acid is about 5 mg/d, it may be predicted that with a severe dietary deficiency, 5 to 6 weeks would be required before clear signs of deficiency are observed. This is based on the estimate that daily excretion of 5 mg represents a 1% to 2% loss of the total body pool of pantothenic acid. Consistent with this estimate, limited studies in humans indicate that about 6 weeks of severe depletion are

Table 4. Effects of Pantothenic Acid Deficiency in Selected Species

Species	Symptoms
Chicken	Dermatitis around beak, feet, and eyes; poor feathering; spinal cord myelin degeneration; involution of the thymus; fatty degeneration of the liver[2-4,49-51]
Rat	Dermatitis; loss of hair color; loss of hair around the eyes; hemorrhagic necrosis of the adrenals; duodenal ulcer; spastic gait; anemia; leukopenia; impaired antibody production; gonadal atrophy with infertility[52-56]
Dog	Anorexia; diarrhea; acute encephalopathy; coma; hypoglycemia; leukocytosis; hyperammonemia; hyperlactemia; hepatic steatosis; mitochondrial enlargement[57,58]
Pig	Dermatitis; hair loss; diarrhea with impaired sodium, potassium, and glucose absorption; lachrymation; ulcerative colitis; spinal cord and peripheral nerve lesions with spastic gait[59,60]
Human	Numbness and burning of feet and hands; headache; fatigue; insomnia; anorexia with gastric disturbances; increased sensitivity to insulin; decreased eosinopenic response to adrenocorticotropic hormone; impaired antibody production[61-63]

required before urinary pantothenic acid decreases to a basal level of excretion.[64-66]

Because pantothenic acid is such a ubiquitous component of foods, both animal and vegetable, deficiency in humans is very rare. If present, pantothenic acid deficiency is usually associated with multiple nutrient deficiencies, thus making it difficult to discern effects specific to a lack of pantothenic acid. What is known about pantothenic acid deficiency in humans comes primarily from two sources of information. First, during World War II, malnourished prisoners of war in Japan, Burma, and the Philippines experienced numbness and burning sensations in their feet. While these individuals suffered multiple deficiencies, this specific syndrome was only reversed upon pantothenic acid supplementation.[61] Second, experimental pantothenic acid deficiency has been induced in both animals and humans by the administration of the pantothenic acid kinase inhibitor ω-methylpantothenate, in combination with a diet low in pantothenic acid.[62,63,67] Observed symptoms in humans included numbness and burning of the hands and feet similar to that experienced by the World War II prisoners of war, as well as a myriad of other symptoms listed in Table 4. Some of the same symptoms are produced when individuals are fed a semisynthetic diet from which pantothenic acid has been essentially eliminated, but without the addition of ω-methylpantothenate.[64] Another pantothenic acid antagonist, calcium hopantenate, has been shown to induce encephalopathy with hepatic steatosis and a Reye's-like syndrome in both dogs and humans.[68,69] Oral pantothenic acid, even in doses as high as 10 to 20 g/d, is well tolerated[70,71]; however, occasional mild diarrhea may occur.

Status Determination

Pantothenic acid status is reflected by both whole-blood concentration and urinary excretion. As cited above, whole-blood concentrations typically range from 1.6 to 2.7 μmol/L,[48] and a value under 1 μmol/L is considered low. Urinary excretion is considered a more reliable indicator of status because it is more closely related to dietary intake.[37,47,62-64] Excretion of less than 1 mg of pantothenic acid per day in urine is considered low. Plasma level of the vitamin is a poor indicator of status because it is not highly correlated with changes in intake or status.[43,72]

Pantothenic acid concentrations in whole blood, plasma, and urine are measured by microbiological assay employing *Lactobacillus plantarum*. For whole blood, enzyme pretreatment is required to convert CoA to free pantothenic acid because *L. plantarum* does not respond to CoA. Other methods that have been employed to assess pantothenic acid status include radioimmunoassay, enzyme-linked immunosorbent assay, and gas chromatography. The topic of pantothenic acid status assessment has been reviewed previously.[72]

Health Claims

With the rapid development of the Web, information about dietary supplements and their putative health benefits can be and is disseminated to the general public with an ease and pace never before possible. However, many health claims for dietary supplements have little or no scientific basis. Although overt deficiency of pantothenic acid is extremely rare in humans, a Web search for "pantothenic acid" reveals numerous websites providing background information, health claims, and, of course, an opportunity to buy the vitamin for oral consumption. Some of the claims made on these websites are completely unwarranted. For example, the use of pantothenic acid to prevent and treat graying hair was based on the observation that pantothenic acid deficiency in rodents causes their fur to turn gray.[53] No association between graying of hair in humans and pantothenic acid status has ever been demonstrated. In contrast, some claims for pantothenic acid have a more credible scientific basis and are worthy of review.

Cholesterol Lowering

Pantothenic acid is not particularly effective in lowering serum cholesterol levels. Rather, oral doses of its metabolite, pantetheine, or more specifically the dimer, pantethine, induce favorable effects on serum cholesterol concentrations. Several studies have indicated that pantethine, in doses typically ranging from 500 to 1200 mg/d, can lower total serum cholesterol, low-density lipoprotein cholesterol, and triacylglycerols, and raise high-density lipoprotein cholesterol in individuals with dyslipidemia, hypercholesterolemia, and hyperlipoproteinemia associated with diabetes.[73-78] The effects are very favorable compared with those of the more conventional lipid-lowering drugs, such as lovastatin, which tend to be associated with significant side effects and potential liver toxicity. In contrast, there appear to be no adverse effects associated with high-dose pantethine therapy. Furthermore, evidence exists that pantethine therapy is more effective than dietary modification in reducing serum cholesterol and lipid concentrations.[73] The mechanism by which pantethine exerts its hypolipemic effects is unclear. A hypothesized site of action is in the regulation of liver sterol biosynthesis. Because pantethine is a coenzyme precursor, it may shunt active acetate from sterol synthesis to mitochondrial oxidative and respiratory pathways.[79] Additionally, pantethine may promote improved triacylglycerol and low-density lipoprotein cholesterol catabolism, as well as reduced cholesterol synthesis via inhibition of the enzyme hydroxymethyl glutaryl-CoA-reductase.[80-82]

Enhancement of Athletic Performance

Scientific support for an effect of pantothenic acid supplements on athletic performance is limited. Until recently, most of the potential benefit has been inferred from animal studies. More than 60 years ago, frog muscles soaked in pantothenic acid solution were shown to do

twice as much work as control muscles before giving out,[83] and more than 30 years ago, rats supplemented with high doses of pantothenic acid were shown to withstand exposure to cold water longer than unsupplemented rats.[84] Moreover, rats deficient in pantothenic acid became exhausted more rapidly during exercise than did replete controls.[85] In this latter study, deficiency was associated with lower tissue CoA concentrations and greater depletion of glycogen reserves during exercise.

Studies assessing the influence of pantothenic acid on human performance are mixed. In one study, well-trained distance runners were supplemented with 2 g/d of pantothenic acid for 2 weeks.[86] These athletes outperformed other equally well-trained distance runners who received placebo. Those who received the supplements also used 8% less oxygen to perform equivalent work and had about 17% less lactic acid accumulation. These differences, particularly in the context of athletic competition, are potentially significant. However, in a separate study, no effect on performance was observed in highly conditioned distance runners after receiving 1 g/d of pantothenic acid for 2 weeks.[87] Additionally, no difference in performance was observed among highly trained cyclists given either a combination of thiamin (1 g) and pantethine/pantothenic acid (1.9 g) or placebo. The supplement or placebo was given for 7 days before each exercise test. The investigators found no effect on any physiological or performance parameters during steady-state or high-intensity exercise.[88] Further research is warranted in this area, including investigation into whether performance can be enhanced for average individuals, as well as elite athletes working at the limits of human performance.

Rheumatoid Arthritis

Over 50 years ago, researchers noted that young rats made acutely deficient in pantothenic acid suffered defects in growth and development of bone and cartilage that were reversed by repletion of the vitamin.[89] Subsequently, blood levels of pantothenic acid in humans with rheumatoid arthritis were found to be lower than in healthy controls. On the basis of this finding, an unblinded trial was conducted in which 20 patients with rheumatoid arthritis were injected daily with 50 mg of calcium pantothenate.[90] Blood levels of pantothenic acid increased to normal, and relief from rheumatoid symptoms was achieved in most cases. Symptoms recurred when supplementation was discontinued. Similar results were obtained in arthritic vegetarians.[90] In 1980, it was reported in a double-blind, placebo trial that oral doses of calcium pantothenate ($\leq$2 g/d) reduced the duration of morning stiffness, degree of disability, and severity of pain in patients with rheumatoid arthritis.[91] Individuals with other forms of arthritis were not helped by the supplements, indicating that a therapeutic effect of pantothenic acid may be specific for rheumatoid arthritis. No other published studies are available to confirm this potential benefit.

Wound Healing

Oral administration of pantothenic acid and application of pantothenol ointment to the skin have been shown to accelerate the closure of skin wounds and increase the strength of scar tissue in animals. Adding calcium D-pantothenate to cultured human skin cells given an artificial wound increased the number of skin cells and the distance that they migrated across the edge of the wound.[92] These effects are likely to accelerate wound healing. Little in vivo data, however, exist for humans to support the findings of accelerated wound healing in cell culture and animal studies. A randomized, double-blind study examining the effect of supplementing patients undergoing surgery for tattoo removal with 1000 mg of vitamin C and 200 mg of pantothenic acid did not demonstrate any significant improvement in the wound healing process in those who received the supplements.[93] Furthermore, no benefits were observed when the doses were increased to 3000 mg of ascorbic acid and 900 mg of pantothenic acid.[94] A topical form of pantothenic acid, panthenol or dexapanthenol, appears to play some role in the management of minor skin disorders. Dexapanthenol may help maintain skin hydration in cases of radiation dermatitis,[95] a frequent side effect of radiation therapy for cancer, and may reduce skin irritation caused by experimental sodium lauryl sulfate exposure.[96] Dexpanthenol has also been recommended to treat cheilitis (chapped lips) and dry nasal mucosa associated with treatment with the acne drug isotretinoin.[97]

Lupus Erythematosus

It has been hypothesized by Leung[98] that lupus erythematosus, a systemic autoimmune disorder that affects the skin, joints, and various internal organ systems, may be the result of pantothenic acid deficiency. The hypothesis is based on the supposition that pantothenic acid deficiency may be induced by three drugs—procainamide, hydralazine, and isoniazid—that are also known to cause drug-induced lupus erythematosus. These drugs are metabolized via CoA-dependent acetylation, and the increased demand for CoA may cause pantothenic acid deficiency. However, no data have been generated on the effect of these drugs on cellular CoA or pantothenic acid concentrations. Leung further postulated that non-drug-induced systemic lupus erythematosus may be the consequence of an increased need for pantothenic acid in susceptible individuals with genetic polymorphisms in CoA-dependent enzymes.[98] Such polymorphisms remain to be identified. Nonetheless, Leung recommended that lupus erythematosus be treated with a combination of vitamins and minerals, including 10 g/d of pantothenic acid.[98]

Support for such pharmacological doses comes from studies carried out in the 1950s. Some, but not all, symptoms of lupus erythematosus were alleviated with high doses (8–15 g/d) of pantothenic acid derivatives (calcium pantothenate, panthenol, or sodium pantothenate) alone[99] or in combination with vitamin E supple-

ments.[100,101] No improvements in disease symptoms were observed with lower doses (400–600 mg) of calcium pantothenate.[102] With modern technology available to probe genes for polymorphic variability, studies in lupus erythematosus patients should be repeated to test the hypothesis that a genetic-based increased requirement of pantothenic acid underlies the pathogenesis of this disease.

Summary and Future Directions

Identified almost 60 years ago, pantothenic acid is an essential vitamin that serves as the metabolic precursor for CoA. In the form of CoA and as a component of ACP, pantothenic acid is a participant in a myriad of metabolic reactions involving lipids, proteins, and carbohydrates. Though essential, pantothenic acid deficiency in humans is rare due to its ubiquitous distribution in foods of both animal and plant origin. Pantothenic acid supplementation above and beyond adequate dietary intakes may be beneficial for such purposes as cholesterol lowering, enhanced athletic performance, relief from the symptoms of rheumatoid arthritis and lupus erythematosus, and wound healing, but further investigation into these and other health claims is necessary.

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