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PANTOTHENIC ACID

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Summary

Identified almost 60 years ago, pantothenic acid is an essential vitamin, which serves as the metabolic precursor for coenzyme A. In the form of coenzyme A and as a component of acyl carrier protein, 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 owing to its ubiquitous distribution in foods of both animal and plant origin. Pantothenic acid supplementation may have some efficacy, but further investigation into various health claims is necessary before any specific recommendations can be given.

Introduction

The discovery of pantothenic acid followed the same path that led to the discovery of other water-soluble vitamins, i.e. 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.* (1933) established that pantothenic acid was required for the growth of certain bacteria and yeast. Next, Elvehjem and associates (Wooley *et al.*, 1939) and Jukes and associates (Jukes *et al.*, 1939; Spies *et al.*, 1940) 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 (Williams *et al.*, 1933; Williams and Majors, 1940). 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, i.e. 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 as starting material (Williams and Majors, 1940). With this

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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, was discovered as the cofactor essential for the acetylation of sulfonamides and choline (Plesofsky-Vig and Brambi, 1988). In the mid-1960s, pantothenic acid was next identified as a component of acyl carrier protein (ACP) in the fatty acid synthesis complex (Wakil, 1989). 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, provide 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 24.1A). Metabolic processing of pantothenic acid, described in detail below, produces the important intermediate, 4′-phosphopantetheine (Figure 24.1B), 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 24.1C). Further metabolic processing with the addition of adenine and ribose 3′-phosphate produces the essential cofactor, coenzyme A (CoA) (Figure 24.1D).

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 because it has greater stability than the pure acid (Bird and Thompson, 1967). 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, though the origin of this designation is obscure.

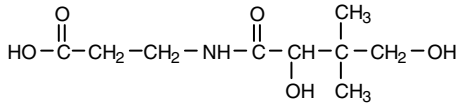
Intestinal Absorption, Cellular Uptake and Efflux, Plasma Transport, and Excretion

The vast majority of pantothenic acid in food is present as a component of CoA or 4′-phosphopantetheine. In order to be absorbed, these substances must first be hydrolyzed (Shibata *et al.*, 1983). 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 further metabolized to pantothenic acid by a third intestinal hydrolase, pantetheinase. In rats, pantothenic acid absorption was initially found to occur in all sections of the small intestine by simple diffusion (Shibata *et al.*, 1983). However, subsequent work in rats and chicks indicated that at low concentrations the vitamin is absorbed by a saturable, sodium-dependent transport mechanism (Fenstermacher and Rose, 1986), sometimes referred to as the sodium-dependent multivitamin transporter (SMVT), which is shared with biotin (Said, 1999). In vitro experiments utilizing Caco-2 cell monolayers as a model of intestinal absorption established that pantothenic acid uptake is inhibited competitively by biotin, and vice versa (Said, 1999).

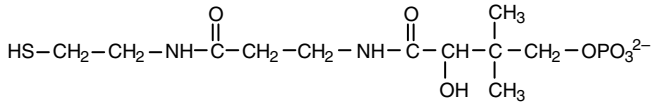
After absorption, pantothenic acid enters the circulation from which it is taken up by cells in a manner similar to that of intestinal absorption (Spector and Mock, 1987; Beinlich *et al.*, 1990; Grassl, 1992). The process for pantothenic acid cellular uptake appears saturable with an apparent K_m of 15–20 μM. Transport across cell membranes occurs by carrier-mediated, sodium gradient-dependent and electroneutral mechanisms (Smith and Milner, 1985; Lopaschukf *et al.*, 1987; Beinlich *et al.*, 1989, 1990; Said *et al.*, 1998). Pantothenic acid cellular uptake has also been linked to protein kinase C (PKC) and calmodulin-dependent regulatory and signaling pathways (Lopaschukf *et al.*, 1987). The dependence on PKC is based on observations that pretreatment of cells with a PKC activator, such as phorbol 12-myristate 13-acetate (PMA) 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 cellular 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 (Lopaschukf *et al.*, 1987). That active uptake of pan-

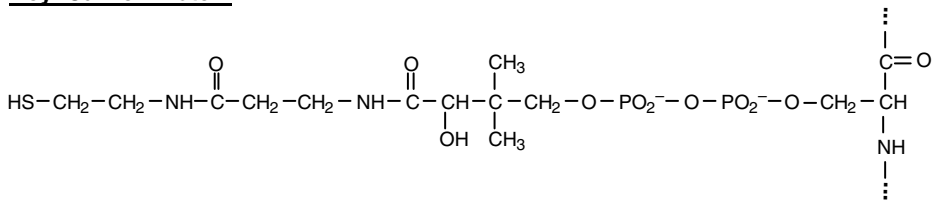
A. Pantothenic Acid



B. 4'-Phosphopantetheine



C. Acyl Carrier Protein



D. Coenzyme A

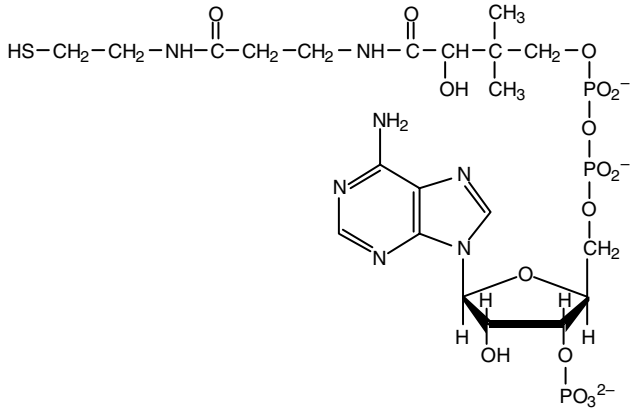


FIG. 24.1 Chemical structures of pantothenic acid, 4′-phosphopantetheine, acyl carrier protein, and coenzyme A.

tothenic acid is important 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 10–15 μM and in the heart ~100 μM compared with 1–5 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 (Spector, 1986, 1987). For comparison, the concentrations of CoA and ACP are 50–100 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, i.e. 70–90% of the total cellular CoA content.

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.

Cellular Regulation and Functions

CoA and ACP 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 24.2). The first step is phosphorylation of pantothenic acid to 4′-phosphopantothenic acid by pantothenic acid kinase (Fisher *et al.*, 1985; Rock *et al.*, 2000). Three distinct types of pantothenic acid kinase (PanK) have been identified. PanK-I and III are found in bacteria. PanK-II is mainly found in eukaryotes and occurs in four different isoforms (PanK1, PanK2, PanK3, and PanK4) (Leonardi *et al.*, 2005). Pantothenic acid kinase possesses a broad pH optimum (between pH 6 and 9) with a K_m for pantothenic acid of ~20 μM. Mg-ATP is used as the nucleotide substrate for this phosphorylation reaction with a K_m of ~0.6 mM.

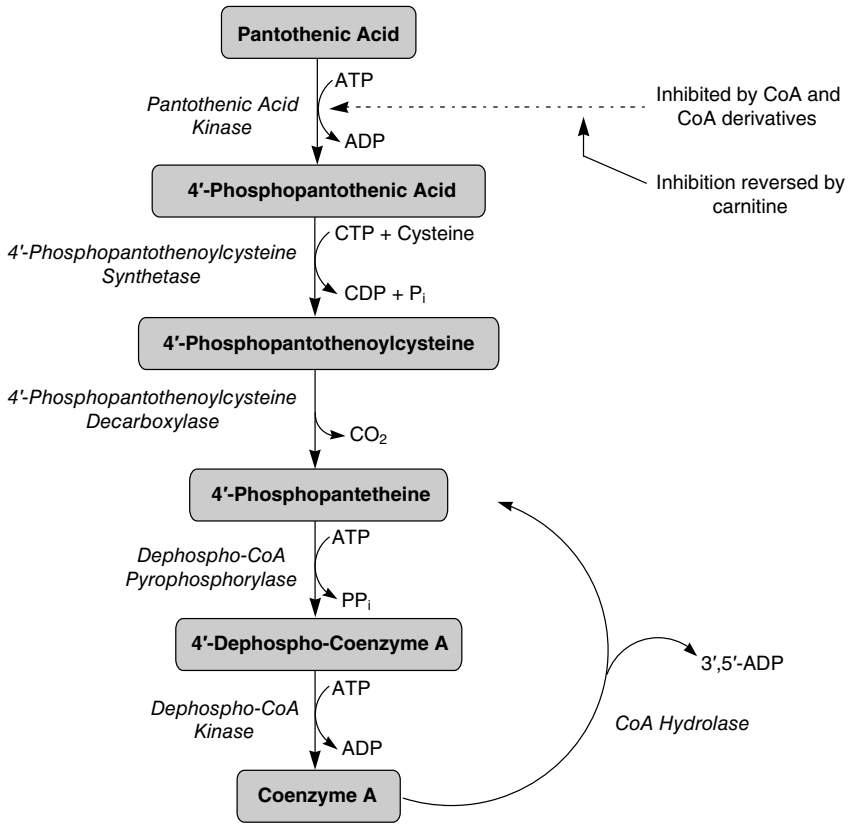


FIG. 24.2 Metabolic conversion of pantothenic acid to coenzyme A.

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 non-specifically by various anions (e.g. thiazolidinediones, sulfonylureas, and steroids are inhibitors and fatty acyl-amides and tamoxifen are activators) (Leonardi *et al.*, 2010). In cells, feedback inhibition of the kinase by CoA or CoA derivatives governs flux through the subsequent steps in the CoA synthesis pathway and defines the upper threshold for intracellular CoA cofactor levels. Inhibition by acetyl-CoA is 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. Substrates are added to pantothenic acid kinase sequentially with ATP as the leading substrate. The allosteric regulatory domain responsible for acetyl-CoA inhibition also binds the substrates, pantothenate and pantetheine, and the various small molecule inhibitors and activators that can influence pantothenic acid kinase activity. Thus, descriptive features of mechanisms involving pantothenic acid kinase at the substrate level are often complex.

Of interest, L-carnitine, important for the transport of fatty acids into mitochondria, is a non-essential activator of pantothenic acid kinase. Carnitine has no effect by itself, but specifically reverses the inhibition by CoA. In heart, 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 regulation of cellular pantothenic acid content, i.e. 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 (Fisher *et al.*, 1985). The ratio of free to acylated carnitine varies considerably depending on feeding and hormonal influences, with insulin particularly important. Fasting and type 1 diabetes (states of low insulin) increase pantothenic acid kinase activity and the total content of CoA (Reibel *et al.*, 1981; Robishaw *et al.*, 1982; Kirschbaum *et al.*, 1990). In addition, 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 (~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 coenzyme A 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 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 24.2) (Bucovaz *et al.*, 1998).

ACP is sometimes referred to as a "macro-cofactor," because, in bacteria, yeast and plants, it is composed of a polypeptide chain (MW ~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 (MW ~250 000 Da each). The carrier segment or domain of the fatty acid synthetic complex is also called acyl carrier protein, i.e. 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 holoACP peptide or domain formation, the 4′-phosphopantetheine transferase gene has been cloned from a human source (Praphanphoj *et al.*, 2001). Although data are limited on phosphopantetheine transferase and ACP regulation in animals, in plants the addition of exogenous CoA to intact chloroplasts stimulates the conversion of apoACP to holoACP. It should also be appreciated that, in addition to fatty acid synthesis, phosphopantetheine transferase catalyzes the transfer of 4′-phosphopantetheine from CoA to other proteins. For example, it has been shown that in human cell lines one of the enzymes of folate metabolism, 10-formyltetrahydrofolate dehydrogenase (FDH), requires

TABLE 24.1 Selected functions of CoA and ACP

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

a 4′-phosphopantetheine prosthetic group to aid the conversion of 10-formyltetrahydrofolate to tetrahydrofolate and CO_2 (Strickland *et al.*, 2010).

As an additional point, various agonists of fatty acid catabolism can affect CoASH-related metabolism. Peroxisome proliferator-activated receptors, such as PPARα, when activated are often related to an increase in fatty acid β-oxidation. Targets of PPARα also influence PanK and genes encoding proteins involved in the transport and synthesis of acylcarnitines. Using state-of-the-art metabolomic approaches (e.g. high-resolution NMR and mass spectrometry technology), it has been shown in humans that significant depletion of both pantothenic acid (as much as five-fold) and acetylcarnitine (as much as 20-fold) occurs in response to PPAR agonists, such as fenofibrate, based on analysis of urinary metabolites (Patterson *et al.*, 2009). As a transcriptional regulator, PPARα includes pantothenate kinase and genes encoding proteins involved in the transport and synthesis of acylcarnitines.

Selected Functions of CoA and ACP

Important functions of CoA and ACP are listed in Table 24.1. Principally, CoA is involved in acetyl and acyl transfer reactions and processes related to oxidative metabolism and catabolism, whereas ACP is involved primarily 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 24.2. 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 acyl carrier protein acts as a transmethylation inhibitor in porcine liver (Seo *et al.*, 2002). ACP is also structurally homologous to acidic ribosomal structural proteins, e.g. ribosomal protein P2 (Raychaudhuri and Rajasekharan, 2003). Moreover, in bacteria and plants, ACP is important in a number of pathways, such as amino acid synthesis and 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 (Khosla and Tang, 2005).

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

TABLE 24.2 Catalytic sites associated with the fatty acid synthase complex

Enzyme	Catalytic function
1. Acetyl transferase	Catalyzes the transfer of an activated acetyl group on CoA to the sulfhydryl group of 4′-phosphopantetheine (ACP domain). In a subsequent step, the acetyl group is transferred to a second cysteine-derived sulfhydryl group near the active site of 3-oxoacyl synthase (see step 3) leaving the 4′-phosphopantetheine sulfhydryl group free for step 2
2. Malonyl transferase	Catalyzes the transfer of successive incoming 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-oxobutyryl (acetoacetyl) derivative. In the second through the seventh cycles, it is the newly formed acyl moieties that attack 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, hydroxy fatty acids
5. 3-Hydroxyacyl dehydratase	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 sulfhydryl group adjacent to 3-oxoacyl synthase, as described in step 1, until a 16-carbon palmitoyl group is formed. This group, still attached to the 4′-phosphopantetheine arm, is the highly specific substrate for the remaining enzyme of the complex, thioester hydrolase
7. Thioester hydrolase	Liberates palmitic acid (step 6) from the 4′-phosphopantetheine arm

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 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, consider that, at pH 7.0, the -ΔG of hydrolysis is ~7.5 kcal for acetyl-CoA and 10.5 kcal for acetoacetyl-CoA compared with 7–8 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 (Nicholis and Ferguson, 2002).

Dietary Sources and Requirements

Pantothenic acid is found in a wide variety of foods of both plant and animal origin at levels in the range 20–50 μg/g. Particularly rich sources of pantothenic acid include chicken, beef, liver and other organ meats, whole grains, potatoes, and tomato products (Walsh *et al.*, 1981). Royal bee jelly and ovaries of tuna and cod also have high levels of the vitamin (Robinson, 1966). 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 37–47% loss of pantothenic acid, while canning of meats, fish, and dairy products leads to losses of 20–35% (Schroeder, 1971). Greater losses of the vitamin occur during canning (46–78%) and freezing (37–57%) of vegetables. Pantothenic acid is also synthesized by intestinal microorganisms (Stein and Diamond, 1989), though 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 10–20 μM. At an intake of ~10–15 mg

TABLE 24.3 Adequate intakes (AIs) for pantothenic acid

Age group	AI (mg/day)
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
Pregnancy	6.0
Lactation	7.0

Data from Institute of Medicine, 1988.

of CoA, the amount of CoA in a typical meal, the pantothenic acid concentration in luminal fluid would be ~1–2 μM. At this concentration, pantothenic acid would not saturate the transport system, and as a consequence should be efficiently and actively absorbed (Said, 1999).

A dietary reference intake has yet to be established for pantothenic acid. Adequate intakes (AI) for men and women throughout the life-cycle have been suggested based on observed mean intakes and estimates of basal excretion in urine (Table 24.3) (Institute of Medicine, 1988). Urinary excretion of pantothenic acid only exceeds basal levels when intakes are greater than 4 mg/day in young adult males. Thus, an intake of 4 mg/day likely reflects the level at which saturation of the body pool occurs (Tarr *et al.*, 1981). Estimates of dietary intake in healthy adults have ranged from 4 to 7 mg/day (Srinivasan *et al.*, 1981; Tarr *et al.*, 1981; Bull and Buss, 1982; Kathman and Kies, 1984). There is no evidence to suggest that this range of intake is inadequate, and 5 mg/day has been set as the AI for adults. For adults older than 51 years, the AI remains the same (5 mg/day) as there is currently no basis for expecting an increased requirement in elderly individuals. During pregnancy, the AI is increased to 6 mg/day based on usual intakes of 5.3 mg/day (Song *et al.*, 1985) with rounding up. During lactation, the AI is increased further to 7 mg/day, accounting for additional secretion of the vitamin in human milk (1.7 mg/day) and the lower maternal blood concentrations reported when intakes are about 5–6 mg/day (Deodhar and Ramakrishnan, 1961; Cohenour and Calloway, 1972; Song *et al.*, 1985). This is likely the result of efficient sequestering of the vitamin in human milk, estimated to be 0.4 mg for every 1 mg pantothenic acid consumed during active lactation (Song *et al.*, 1984).

The AI for infants reflects the mean intake of infants fed principally with human milk. Human milk contains about 5–6 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 (Kerrey *et al.*, 1968). Dietary intake of pantothenic acid was 3.8 and 5 mg/day in children of high and low socioeconomic status, respectively, and urinary excretion was 3.36 and 1.74 mg/day, respectively. In a separate study, 35 healthy girls, 7–9 years of age, were fed defined diets, and urinary excretion was measured (Pace *et al.*, 1961). The average daily excretion was 1.3 mg/day when intake was 2.79 mg/day, and 2.7 mg/day when intake was 4.45 mg/day. Therefore, intakes of 2.8–4.5 mg/day 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/day for males and 4.1 mg/day for females (Eissenstat *et al.*, 1986). Average urinary excretion in this latter study was 3.3 and 4.5 mg/day 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 (Wittwer *et al.*, 1989). Taken together, these data indicate that intake of 4 mg/day is sufficient to maintain normal blood concentrations in adolescents.

Using the estimate of 20–50 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 100–200 g of solid food, i.e. the equivalent of a mixed diet corresponding to 600–1200 kcal or 2.4–4.8 MJ. The typical western diet contains 6 mg or more of available pantothenic acid (Tarr *et al.*, 1981). For a more detailed review of the AI for pantothenic acid, see Institute of Medicine (1988).

Deficiency and Toxicity

The essentiality of pantothenic acid has been documented in a wide variety of animal species. The classical signs

TABLE 24.4 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 (Jukes, 1939; Wooley *et al.*, 1939; Spies *et al.*, 1940; Kratzer and Williams, 1948; Milligan and Briggs, 1949; Gries and Scott, 1972)
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 (Subba Row and Hitchings, 1939; Sullivan and Nicholls, 1942; Axelrod, 1971; Eida *et al.*, 1975; Pietrzik *et al.*, 1975)
Dog	Anorexia; diarrhea; acute encephalopathy; coma; hypoglycemia; leukocytosis; hyperammonemia; hyperlactemia; hepatic steatosis; mitochondrial enlargement (Schaefer *et al.*, 1942; Noda *et al.*, 1991)
Pig	Dermatitis; hair loss; diarrhea with impaired sodium, potassium, and glucose absorption; lachrymation; ulcerative colitis; spinal cord and peripheral nerve lesions with spastic gait (Wintrobe *et al.*, 1943; Nelson, 1968)
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 (ACTH); impaired antibody production (Glusman, 1947; Hodges *et al.*, 1958, 1959)

of deficiency, first recognized by Elvehjem, Jukes and colleagues in chickens, include growth retardation and dermatitis (Jukes, 1939; Wooley *et al.*, 1939; Spies *et al.*, 1940). 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 24.4 (Subba Row and Hitchings, 1939; Schaefer *et al.*, 1942; Sullivan and Nicholls, 1942; Wintrobe *et al.*, 1943; Glusman, 1947; Kratzer and Williams, 1948; Milligan and Briggs, 1949; Hodges *et al.*, 1958, 1959; Nelson, 1968; Axelrod, 1971; Gries and Scott, 1972; Eida *et al.*, 1975; Pietrzik *et al.*, 1975; Noda *et al.*, 1991).

Assuming that the human adult requirement for pantothenic acid is ~5 mg/day, it may be predicted that, with a severe dietary deficiency, 5–6 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 1–2% 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 required before urinary pantothenic acid decreases to a basal level of excretion (Fox and Linkswiler, 1961; Fry *et al.*, 1976; Annous and Song, 1985).

Because pantothenic acid is such a ubiquitous component of foods, both animal and vegetable, deficiency of this vitamin 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. 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 (Glusman, 1947). Experimental pantothenic acid deficiency has also been induced in both animals and humans by administration of the pantothenic acid kinase inhibitor, ω-methylpantothenate, in combination with a diet low in pantothenic acid (Drell and Dunn, 1951; Hodges *et al.*, 1958, 1959). 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 24.4. Some of the same symptoms are produced when individuals are fed a semi-synthetic diet from which pantothenic acid has been essentially eliminated, but without addition of ω-methylpantothenate (Fry *et al.*, 1976). Another pantothenic acid antagonist, calcium hopantenate, has been

shown to induce encephalopathy with hepatic steatosis and a Reye-like syndrome in both dogs and humans (Noda *et al.*, 1988, 1991).

Further evidence of the essentiality of pantothenic acid metabolism is revealed by an autosomal recessive disorder, initially called Hallervorden-Spatz syndrome and subsequently referred to as pantothenate kinase-associated neurodegenerative disease or neurodegeneration with brain-iron accumulation-1 (Zhou *et al.*, 2001; Hayflick *et al.*, 2003; Johnson *et al.*, 2004; Gregory *et al.*, 2009). Mutations in the gene encoding PANK2 (gene map locus: 20p13-p12.3) underlie this disorder, which is characterized by iron accumulation in the brain, progressive neurodegeneration, and early death. The pathogenesis of the disorder is believed to be related to mitochondrial CoA deficiency, inhibition of fatty acid β-oxidation, and oxidative stress. In addition, lack of phosphopantothenic acid synthesis may lead to accumulation of cysteine, the substrate required for step 2 of pantothenic acid metabolism, i.e. synthesis of phosphopantothenoylcysteine (Figure 24.2). It has been proposed that accumulated cysteine rapidly auto-oxidizes in the presence of free iron, leading to the generation of free radicals and additional oxidative stress (Zhou *et al.*, 2001; Johnson *et al.*, 2004).

Oral pantothenic acid, even in doses as high as 10–20 g/day, is well tolerated (Ralli and Dumm, 1953; Tahiliani and Beinlich, 1991). 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 (Wittwer *et al.*, 1989), and a value <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 (Hodges *et al.*, 1958, 1959; Fry *et al.*, 1976; Tarr *et al.*, 1981; Eissenstat *et al.*, 1986). Excretion of <1 mg 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 (Cohenour and Calloway, 1972; Sauberlich, 1999).

Pantothenic acid concentrations in whole blood, plasma, and urine are measured by microbiological assay employing *Lactobacillus plantarum*. For whole blood, enzyme pre-treatment is required to convert CoA to free pantothenic acid since *L. plantarum* does not respond to CoA. Other methods that have been employed to assess pantothenic acid status include radioimmunoassay, ELISA, and gas chromatography. The topic of pantothenic acid status assessment has been reviewed (Sauberlich, 1999).

Health Claims

With the rapid development of the internet, information about nutritional supplements and their putative health benefits is disseminated to the general public with an ease and pace never before possible. However, many health claims for nutritional supplements have little or no scientific basis. Although overt deficiency of pantothenic acid is extremely rare in humans, an internet search for "pantothenic acid" reveals numerous websites providing background information, health claims, and of course an opportunity to buy the vitamin for oral consumption. Many 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 (Sullivan and Nicholls, 1942). No association between graying of hair in humans and pantothenic acid status has ever been demonstrated. Moreover, although other claims for pantothenic acid have a more credible scientific basis and are summarized below, it should be noted that many such claims are based on studies that were conducted in the 1940s, 1950s, and 1960s, and still await validation.

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 indicated that pantethine, in doses typically ranging from 500 to 1200 mg/day, 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 (Avogaro *et al.*, 1983; Gaddi *et al.*, 1984; Miccoli *et al.*, 1984; Arsenio *et al.*, 1986; Bertolini *et al.*, 1986; Binaghi *et al.*, 1990). The effects are favorable when compared with those of the more conventional lipid-lowering drugs, such as lovastatin, which may be

associated with side-effects and liver toxicity. There appear to be no adverse side-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 (Avogaro *et al.*, 1983). 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 (Kameda and Abiko, 1980). 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 (Cighetti *et al.*, 1986, 1987, 1988).

Enhancement of Athletic Performance

Scientific support for an effect of pantothenic acid supplements on athletic performance is also 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 exhaustion (Shock and Sebrell, 1944), 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 mice (Ralli, 1968). Moreover, rats deficient in pantothenic acid became exhausted more rapidly during exercise than did pantothenic acid replete controls (Smith *et al.*, 1987). 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/day of pantothenic acid for 2 weeks (Litoff *et al.*, 1985). 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 ~17% less lactic acid accumulation. However, in a separate study, no effect on performance was observed in highly conditioned distance runners after receiving 1 g/day of pantothenic acid for 2 weeks (Nice *et al.*, 1984). 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 (Webster, 1998).

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 (Nelson *et al.*, 1950). 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, a clinical trial was conducted in which 20 patients with rheumatoid arthritis were injected daily with 50 mg calcium pantothenate (Barton-Wright and Elliot, 1963). 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 (Barton-Wright and Elliot, 1963). More recently, it was found in a double-blind, placebo trial that oral doses of calcium pantothenate (≤2 g/day) reduced the duration of morning stiffness, degree of disability, and severity of pain in patients with rheumatoid arthritis (US General Practitioner Research Group, 1980). Individuals with other forms of arthritis were not helped by the supplements, indicating that the therapeutic effect of pantothenic acid is specific for rheumatoid arthritis.

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 (Weimann and Hermann, 1999). 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 that received the supplements (Vaxman *et al.*, 1995). Furthermore, no benefits were observed when the doses were increased to

3000 mg of ascorbic acid and 900 mg of pantothenic acid (Vaxman *et al.*, 1996). A topical form of pantothenic acid, panthenol or dexapanthenol, appears to play some role in the management of minor skin disorders. Dexpanthenol may help maintain skin hydration in cases of radiation dermatitis (Schmuth *et al.*, 2002), and may reduce skin irritation caused by experimental sodium lauryl sulfate exposure (Biro *et al.*, 2003). Dexpanthenol has also been recommended to treat cheilitis and dry nasal mucosa associated with treatment with the acne drug, isotretinoin (Romiti and Romiti, 2002).

Lupus Erythematosus

It has been hypothesized 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 (Leung, 2004). 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. It must be noted, however, that no data have been generated on the effect of these drugs on cellular CoA or pantothenic acid concentrations. It is 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. Such polymorphisms remain to be identified. None the less, it is recommended that lupus erythematosus be treated with a combination of vitamins and minerals, including 10 g/day of pantothenic acid (Leung, 2004). Support for such pharmacological doses comes from studies carried out in the 1950s. Some symptoms of lupus erythematosus, but not all, were alleviated with high doses (8–15 g/day) of pantothenic acid derivatives (calcium pantothenate, panthenol, or sodium pantothenate) alone (Goldman, 1950) or in combination with vitamin E supplements (Welsh, 1952, 1954). No improvements in disease symptoms were observed with lower doses (400–600 mg) of calcium pantothenate (Cochrane and Leslie, 1952). With modern technology available to probe genes for polymorphic variability, supplementation trials 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.

Antimalarial Drugs

More recently, *inhibitors* of the pantothenic acid pathway have been investigated for use as antimalarial drugs, most specifically related to the malaria parasite *Plasmodium falciparum*, which is the most virulent of the *Plasmodium* species in humans. *Plasmodium falciparum* requires an external supply of pantothenic acid to support its intracellular growth (Saliba *et al.*, 2005). Erythrocytes infected with *P. falciparum* rapidly take up pantothenate via the "new permeability pathways" (NPP) induced in the erythrocyte membrane by the maturing parasite (Saliba *et al.*, 1998). This increased permeability of the membrane via the NPP is not present in uninfected erythrocytes. The *P. falciparum* parasite relies on the endogenous synthesis of CoA from pantothenate and does not require exogenous CoA (Bozdech *et al.*, 2003). Thus, the CoA biosynthesis pathway has been a target for antimicrobial drug discovery. The antiplasmodial activity of the many pantothenic acid analogs already available now needs to be determined for *P. falciparum* in vitro in continuous culture. The compounds that are found to be effective at inhibiting the in vitro growth of the parasite should then be tested in a mammalian model. As the spread of the resistance to antimalarial agents widens, the development of new therapies for the treatment and prevention of malaria is essential.

Future Directions

Although CoA and ACP have been the focus of numerous investigations, far less attention has been paid to pantothenic acid. In part this is due to the rarity of naturally occurring pantothenic acid deficiency, and to the fact that descriptions of pantothenic acid deficiency and functions in humans have largely evolved indirectly from the administration of pantothenic acid antagonists; in particular, inhibitors of pantothenic acid kinase. Though these studies were informative, better information is needed regarding pantothenic acid requirements. The Food and Nutrition Board of the Institute of Medicine has yet to consider an RDA, because scientific evidence is currently insufficient for such estimations, although an AI has been set (Table 24.3) (Institute of Medicine, 1988). An RDA has been difficult to establish because CoA and ACP are involved in so many aspects of metabolism that biochemical markers or clinical deficiency criteria *specific* for pantothenic acid deficiency in humans have been difficult to define. In this regard, more information is needed related to the extent

to which dietary pantothenic acid supplementation can stimulate or influence CoA or ACP synthesis.

Another area for future investigation is the potential for pantothenic acid–drug interactions. This could be important given that pantothenic acid and cofactors such as biotin share common receptors (Said *et al.*, 1998). For example, oral contraceptives containing estrogen and progestin may increase the requirement for pantothenic acid (Lewis and King, 1980). Also, though pantetheine has lipid lowering effects (Avogaro *et al.*, 1983; Gaddi *et al.*, 1984; Miccoli *et al.*, 1984; Arsenio *et al.*, 1986; Bertolini *et al.*, 1986; Binaghi *et al.*, 1990), little is known as to whether combining pantetheine with 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins) or nicotinic acid will produce additive effects on blood lipid profiles. In this regard, clinical studies are warranted, as well as basic investigations into the mechanisms of these interactions. The potential for pantothenic acid inhibitors to serve as antimalarial agents is also of great interest for future investigation.

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