9 Pantothenic Acid

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INTRODUCTION AND HISTORY

The discovery of pantothenic acid followed the same path that led to the discovery of other water-soluble vitamins evolving from studies using bacteria and single-cell eukaryotic organisms (e.g., yeast) and eventually animal models [1–23]. Although the widespread occurrence of pantothenic acid in food makes a dietary deficiency unlikely, the use of experimental animal models [5–14], antagonistic analogs, such as ω-methyl-pantothenate [24–29], and in the past several decades, the feeding of semisynthetic diets free of pantothenic acid [25,30–34] have helped to define pantothenate's functions. Largely the efforts of research groups associated with R.J. Williams, C.A. Elvehjem, and T.H. Jukes led to the identification of pantothenic acid as an essential dietary factor. R.J. Williams and coworkers established

that pantothenic acid was required for the growth of certain bacteria and yeast [1,17,20,22,23]. Next, Elvehjem and associates [21] and Jukes and associates demonstrated that pantothenic acid was a growth factor for rats and chicks [2,16,35,36]. Early nutritional studies in animals also demonstrated that there was loss of fur color in black and brown rats and an usual dermatitis that occurred in chickens fed pantothenate-deficient diets; thus, at one point pantothenate was known as the antigray or antidermatitis factor [37].

Williams coined the name pantothenic acid from the Greek meaning "from everywhere" to indicate its widespread occurrence in foodstuffs. The eventual characterization and synthesis of pantothenic acid by Williams in 1940 took advantage of observations that the antidermatitis factor present in acid extracts of various food sources, i.e., pantothenic acid, did not bind to fuller's earth (a highly adsorbent claylike substance consisting of hydrated aluminum silicates) under acidic conditions [22,23]. Using chromatographic and fractionation procedures, which were typical of the 1930s and 1940s (solvent-dependent chemical partitioning), Williams isolated several grams of pantothenic acid for structural determination from 250 kg of liver as starting material [22,23]. With this information, a number of research groups contributed to the chemical synthesis and commercial preparation of pantothenic acid. Pantothenate and its derivatives are now produced mainly through chemical synthesis and the global market in the past decade was $>7 \times 10^6$ kg/year [38].

As emphasized throughout this chapter, pantothenic acid, which is sometimes designated as vitamin B_5, is the core of the structure of coenzyme A (CoA), an essential cofactor in pathways important to oxidative respiration, lipid metabolism, and the synthesis of many secondary metabolites such as steroids, acetylated compounds (e.g., acetylated amino acids, carbohydrates), and prostaglandins and prostaglandin-like compounds. In addition, the phosphopantetheine moiety (a pantothenic acid derivative derived from CoA metabolism) is incorporated into the prosthetic group of the acyl carrier proteins (ACP) used in fatty acid synthases, polyketide synthases, lysine synthesis in yeast and bacteria, and nonribosomal peptide synthetases. Coenzyme A was discovered as the cofactor essential for the acetylation of sulfonamides and choline in the early 1950s [39–42]. In the mid-1970s, pantothenic acid was identified as a component of ACP in the fatty acid synthesis (FAS) complex [43–46]. 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.

CHEMICAL PERSPECTIVES AND NOMENCLATURE

Pantothenic acid [β-alanine-*N*-4-dihydroxy-3,3-dimethyl-1-oxobutyl)-(R); vitamin B_5; CAS Registry Number 79-83-4] is synthesized by microorganisms via an amide linkage of pantoic acid and β-alanine subunits (Figure 9.1). Pantothenic acid is an essential metabolite for all biological systems; however, the biosynthesis of pantothenic acid is limited to plants, bacteria, eubacteria, and archaea (Figure 9.2). It is worth noting that the biosynthesis pathway for pantothenic acid in microorganisms and plants is also viewed as a strong candidate for the discovery of novel antibiotic and herbicidal compounds [38].

Pure pantothenic acid is water soluble, viscous, and yellow. 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 greater stability than the pure acid. The structure elucidation of pantothenate was based on the identification of a lactone formed by degradation of pantothenate. Initial analytical work revealed an α-hydroxy acid that was readily lactonized. Stiller et al. [17] identified the lactone as α-hydroxy-β,β-dimethyl-χ-butyrolactone (pantoyl lactone or pantolactone), which aided in the structural elucidation of pantothenate.

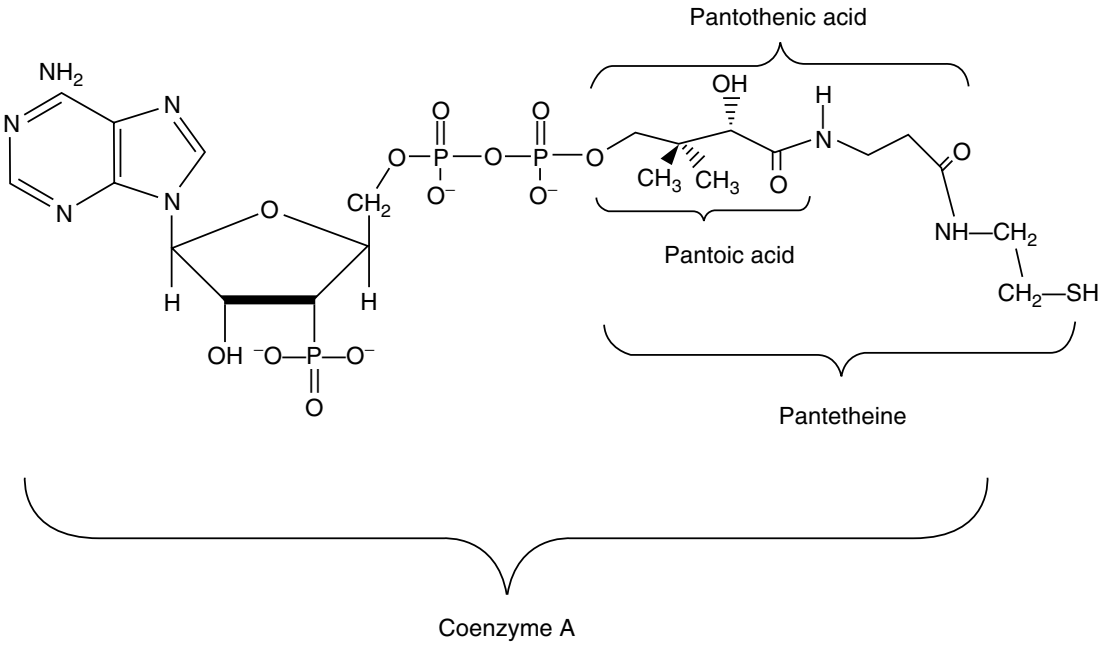


FIGURE 9.1 Structural components of coenzyme A.

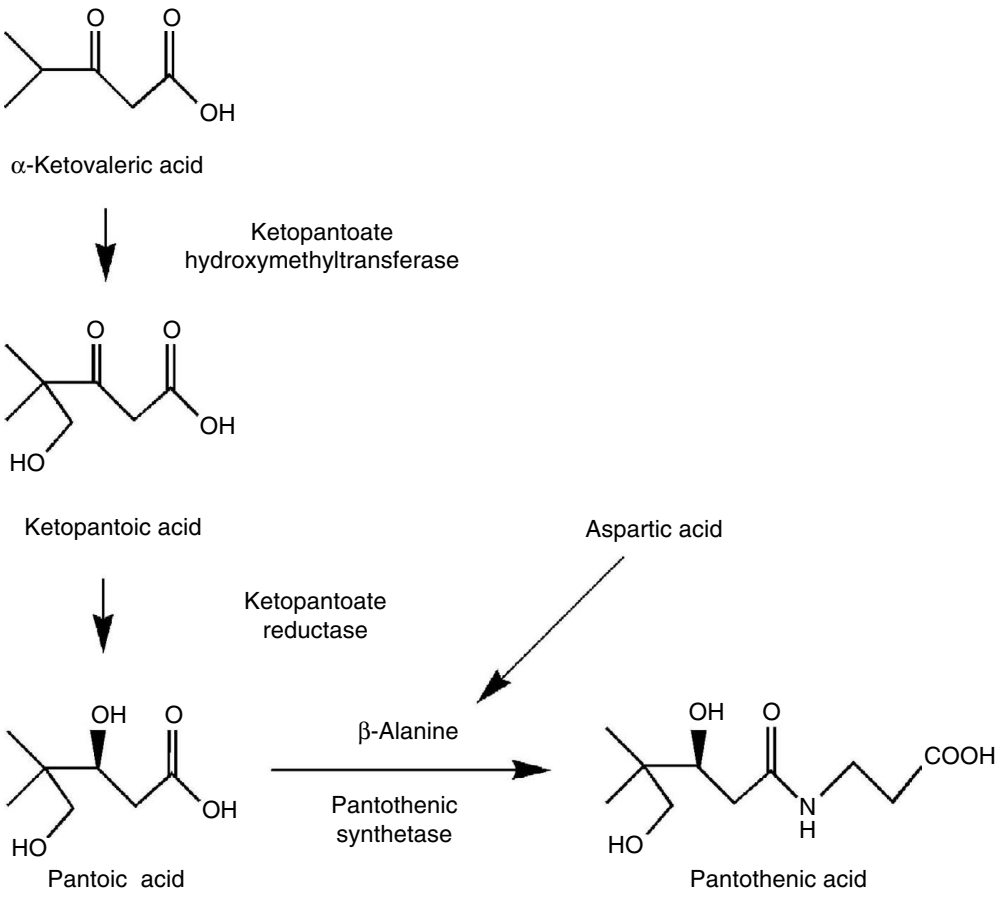


FIGURE 9.2 Pathway for the biosynthesis of pantothenic acid found in plants, bacteria (including archaea), and eubacteria.

FOOD SOURCES AND REQUIREMENTS

Pantothenic Acid Requirements

Although limited, available data suggest that at intakes of 4–6 mg of pantothenic acid per day, serum levels of pantothenic acid are maintained in young adults and no known signs of deficiency are observed. The U.S. recommended dietary allowance (RDA) for pantothenic acid, which is used for determining daily percent values on nutritional supplement and food labels, is 10 mg/day [47].

Pantothenic acid is found in edible animal and plant tissues ranging from 10 to 50 μg/g of tissue. Thus, it is possible to meet the current daily recommended intake for adults with a mixed diet containing as little as 100 to 200 g of solid food; i.e., the equivalent of a mixed diet corresponding to 600 to 1200 kcal or 2.4 to 4.8 MJ. In this regard, the typical Western diet usually contains 6 mg or more of available pantothenic acid [37,48]. Table 9.1 gives the current recommended amounts of pantothenic acid for humans, expressed as dietary reference intakes (DRI) [47]. Moreover, when expressed on a per energy intake equivalent basis, the need for pantothenic acid is remarkably constant across species [49]. Although in mice small amounts of pantothenic acid are synthesized by intestinal bacteria, the contribution of bacterial synthesis to human pantothenic acid status is not known and probably small [28,50]. Regrettably, relatively little quantitative information on the enteric synthesis of pantothenic acid exists.

Food Sources

Chicken, beef, potatoes, oat cereals, tomatoes, eggs, broccoli, and whole grains are major sources of pantothenic acid. Refined grains have a lower content. Table 9.2 contains some typical values for pantothenic acid in selected food. The processing and refining of grains

TABLE 9.1
Pantothenic Acid Dietary Reference Intakes (RDI)[a]

Category	Recommendation
0 through 6 months	1.7 mg/day ~0.2 mg/kg
7 through 12 months	1.8 mg/day ~0.2 mg/kg
Children	
1 through 3 years	2 mg/day
4 through 8 years	3 mg/day
Girls and boys	
9 through 13 years	4 mg/day
14 through 18 years	5 mg/day
Women and men	
19 years and older	5 mg/day
Pregnancy	
14 through 50 years	6 mg/day
Lactation	
14 through 50 years	7 mg/day

Note: There is no evidence of toxicity associated; thus, the lowest observed adverse-effect level (LOAEL) and an associated no observed adverse-effect level (NOAEL) have not been determined.

[a] Recommendation of the Food and Nutrition Board of the Institute of Medicine of the U.S. National Academy of Sciences.

TABLE 9.2
Pantothenic Content in Selected Foods

Ingredient	~Amount (mg/100 g or mL of Edible Portion)
Beer	<0.1
Soft drinks	<0.03
Wine	0.02–0.04
Wheat bran	2–3
Boiled rice	0.2–0.3
Soy flour	1.5–2.5
Raw eggs	1.5–2.0
Cooked fish	0.2–0.5
Lobster	1.5
Oysters	0.5
Salmon	0.5
Tuna	0.4
Apples	0.05
Apricots, bananas	0.1–0.2
Dates	0.8
Grapes	0.04
Lemon and orange juice	0.1
Plums	0.2
Prunes	0.5
Strawberries	0.3
Beef	0.5–1.2
Chicken boiled	0.3–1.0
Liver	5–7
Kidney	4–6
Pork	0.5–1.0
Cheese	1.5
Milk (bovine)	1
Milk (human)	0.3–0.4
Almonds	2–3
Peanuts	2–3
Walnuts	1
Peanut butter	5–8

can produce as much as a 50% loss of pantothenic acid [51–53]. In keeping with the proposed requirements for humans, human milk contains ~5–6 mg of pantothenic acid per 1000 kcal [54–56]. It has been estimated that for every milligram of pantothenic acid consumed in the diet, ~0.4 mg can be transported into milk when lactation is active. Because the pantothenic content of milk correlates well with maternal intakes of pantothenic acid, the possibility does exist that pantothenic acid deficiency may occur in infants consuming milk produced by mothers deficient in the vitamin (e.g., those who consume predominantly refined cereals). Because of the widespread distribution of pantothenic acid in foods and apparently the diets of adults have to be markedly devoid of pantothenic acid to induce deficiency, the need for aggressive fortification of pantothenic acid may never become a high priority.

INTESTINAL ABSORPTION AND MAINTENANCE

The vast majority of pantothenic acid in food is present as CoA or 4′-phosphopantetheine. In order to be absorbed, these substances must first be hydrolyzed [50]. This occurs in the

intestinal lumen by the sequential activity of two hydrolases, pyrophosphatase and phosphatase, with pantotheine as the product. 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. Pantotheine is either absorbed as is, or further metabolized to pantothenic acid by a third intestinal hydrolase, pantothenase [57–60]. In rats, pantothenic acid absorption was initially found to be absorbed in all sections of the small intestine by simple diffusion [28,50,61]. However, subsequent work in rats and chicks indicated that at low concentrations, the vitamin is absorbed by a saturable, sodium-dependent transport mechanism [62]. Further, the overall K_m for pantothenic acid intestinal uptake is 10–20 μM. At an intake of ~10–15 mg of coenzyme A, the amount of coenzyme A 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 should be efficiently and actively absorbed [61].

Researchers have demonstrated that pantothenic acid shares a common membrane transport system in the small intestine with another vitamin, biotin [61,63–67]. Experiments using Caco-2 cell monolayers as a model of intestinal absorption have established that pantothenic acid uptake is inhibited competitively by biotin and vice versa [61,63–67]. Similar relationships were observed in transport experiments involving the blood–brain barrier [61,68,69], heart [70–73], and placenta [74–77]. For example, membrane transport pathways for transplacental transfer of pantothenate were investigated by Grassl [77] assessing the possible presence of a Na^+–pantothenate cotransport mechanism in the maternal facing membrane of human placental epithelial cells. The presence of Na^+–pantothenate cotransport was determined from radiolabeled tracer flux measurements of pantothenate uptake using preparations of purified brush-border membrane vesicles. Compared with other cations, the imposition of an inward Na^+ gradient stimulated vesicle uptake of pantothenate to levels ~40-fold greater than those observed at equilibrium. The effect of biotin on the kinetics of Na^+-dependent pantothenate uptake and the effect of pantothenate on the kinetics of Na^+-dependent biotin uptake suggest that placental absorption of biotin and pantothenate from the maternal circulation also occurs by a common Na^+ cotransport mechanism.

After absorption, pantothenic acid enters the circulation from which it is taken up by cells in a manner similar to that of intestinal absorption (see the following section). The vitamin is excreted in the urine primarily as pantothenic acid [27,78–85]. This occurs after its release from CoA by a series of hydrolysis reactions that cleave off the phosphate and β-mercaptoethylamine moieties.

CELLULAR REGULATION OF PANTOTHENIC ACID, CoA, AND THE IMPORTANCE OF PANTOTHENIC KINASE

Cellular Transport and Maintenance

Said and others [61,63–67] have observed that similar to enterocytes, other epithelial cells take up pantothenic acid in a manner that is inhibited by Na-K-ATPase inhibitors, such as ouabain, and is in competition with biotin. In most instances, activity of this transporter is sensitive to phosphokinase C (PKC)- and A (PKA)-mediated activation and inhibition. For example, pretreatment of epithelial cells with phorbol 12-myristate 13-acetate (PMA), but not with its negative control (4α-PMA) or with 1,2-dioctanoyl-*sn*-glycerol, both activators of PKC, causes significant inhibition in uptake, whereas pretreatment of cells with staurosporine and chelerythrine, inhibitors of PKC, promotes stimulation in uptake [67]. These findings point toward the involvement of a PKC-mediated pathway in the regulation of biotin and pantothenic acid uptake by epithelial cells.

Pantothenic Acid Kinase

Following uptake, the maintenance of pantothenic acid cellular concentration depends on its incorporation into CoASH and pantotheine. The most important control step in this process is the phosphorylation of pantothenic acid to 4′-phosphopantothenic acid by pantothenic acid kinase [86–101] (Figure 9.3). There are four members in the human PanK family: PanK1, PanK2, PanK3, and PanK4, which are located on chromosomes 10q23.31, 20p13, 5q35, and 1p36.32, respectively [98]. Pantothenic acid kinases possess a broad pH optimum (between pH 6 and 9). The K_m for pantothenic acid in the liver enzyme of most animals is ~20 μM. Mg-ATP is the nucleotide substrate for this phosphorylation reaction with a K_m of ~0.6 mM [88,102–112].

The relationships involving the various isoforms are complex. Two murine PanK1s exist, mPanK1α and mPanK1β [86,88,95,97,100]. These two transcripts are the result of an alternate splicing of the same gene. PanK1 localizes predominantly in heart, liver, and kidney [86,88,95,97,100]. PanK2 is ubiquitously expressed with the highest levels in retinal and infant basal ganglia [95,113–115]. PanK3 is limited to the liver, but expressed at a high level [88,95]. The expression of PanK4 occurs in most tissues with a high concentration in muscle [88,95]. Metabolic labeling experiments in rat heart support the role of PanK in controlling the flux of the CoA biosynthesis. For example, enhanced mPanK1β expression reduced the intracellular pantothenate pool and triggered a 13-fold increase in intracellular CoA content. PanK1β activity in vitro was stimulated by CoA and strongly inhibited by acetyl CoA, illustrating the differential modulation of mPanK1β activity by pathway end products and supporting the concept that the expression or activity of PanK is a determining factor in the physiological regulation of the intracellular CoA concentration [100].

Pantothenic acid kinase is activated and inhibited nonspecifically by various anions. More significantly, 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 slightly greater than that of free CoA. The inhibition by free CoA is uncompetitive with respect to pantothenate concentration; K_i for inhibition of 0.2 μM. Interestingly, L-carnitine, important for the transport of fatty acids into mitochondria, is a nonessential activator of pantothenic acid kinase. Carnitine

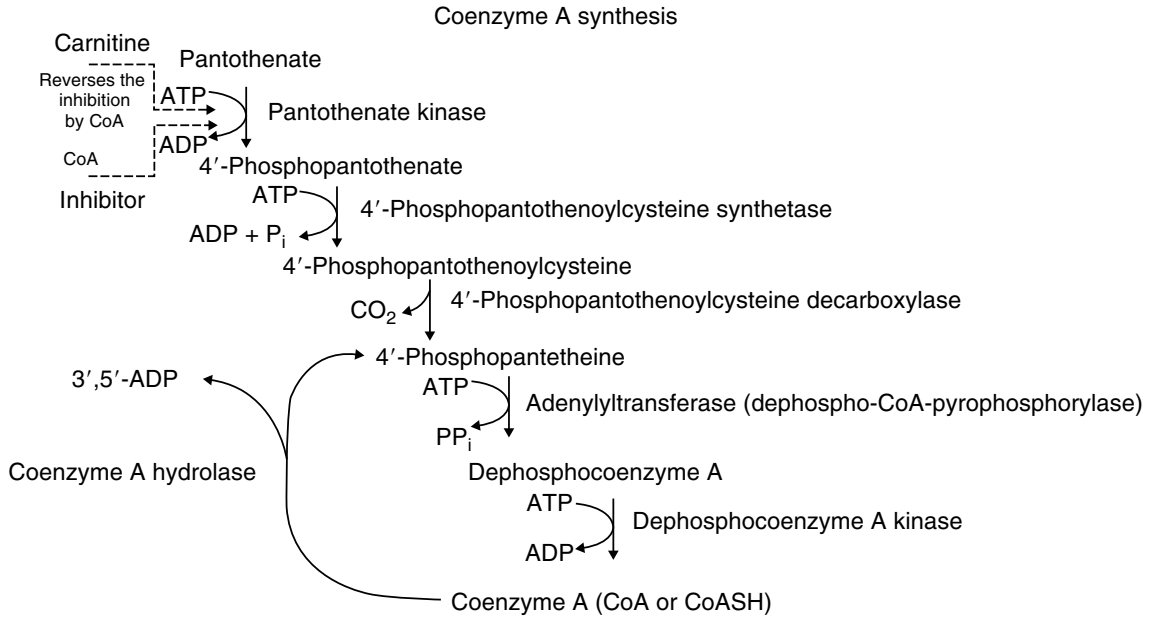


FIGURE 9.3 Coenzyme A metabolism and importance of pantothenic acid kinase.

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 [71,107,108,111,116].

In this regard, 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 [107]. The ratio of free to acylated carnitine varies considerably depending on feeding and hormonal influences, with insulin of particular importance. Fasting and diabetes (states of low insulin) increase pantothenic acid kinase activity and the total content of CoA [102,105,110]. Perfusion of heart preparations or incubation of liver cells with glucose, pyruvate, or palmitate markedly inhibits pantothenic acid phosphorylation because of reduction in free carnitine and increases in the free and acylated forms of CoA [116].

CoA Formation

For CoA synthesis, the additional steps include the addition of adenine and ribose 3′-phosphate to produce CoA composed of 4′-phosphopantetheine linked by an anhydride bond to adenosine 5′-monophosphate, modified by a 3′-hydroxyl phosphate (Figure 9.3). In yeast and perhaps higher organisms (for which details of the pathway require further resolution), these steps are carried out on a protein complex with multifunctional catalytic sites [117–120]. Important enzymatic features of this complex in yeast 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 provides a mechanism by which the 4′-phosphopantetheine can be recycled to form CoA [107–110]. 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. Although some enzymes of the pathway were identified relatively rapidly, it was not possible to identify all enzymes using traditional methods. Hence, the use of bacterial mutants and the application of molecular biology have been essential in resolving key features of the pathway shown in Figure 9.3.

As CoA holds a central position in cellular metabolism, it may therefore be assumed to be an ancient molecule [119]. Starting from the known *Escherichia coli* pathway and known human enzymes required for the biosynthesis of CoA, phylogenetic profiles and chromosomal proximity methods have led to the conclusion that the topology of CoA synthesis from common precursors is essentially conserved across the three domains of life [119].

CoA Regulation

In animal tissue, the levels of CoA cover a wide range and change in response to signals arising from hormones, nutrients, and cellular metabolites. Hepatic CoA levels are among the most responsive to such changes, ranging from 100 to 500 nmol/g liver. In decreasing order: heart > kidney > diaphragm > skeletal muscle contain CoA in concentrations ranging from 100 to 50 nmol/g [43,103,106,108,121,122]. Fasting results in high levels of long-chain fatty acyl CoA thioesters, whereas glucose feeding results in nonacylated CoA derivatives. The total CoA levels decrease in response to insulin, but increase in response to glucagon. The

transfer of activated acyl moieties across organelle membranes, to and from the CoA pools in mitochondria, cytosol, and peroxisomes occurs through the carnitine transferase system and ABC-like transporters [123–125].

The concentration of nonacylated CoA determines the rate of oxidation-dependent energy production in both mitochondria and peroxisomes, and the interorganelle transport of CoA-linked metabolites helps to maintain CoA availability. Although much remains to be investigated regarding the relative roles, various compartments play a role in CoA regulation; available evidence suggests that mitochondria are the principle sites of CoA synthesis. For example, PanK2s localization in mitochondria is proposed to initiate intramitochondrial CoA biosynthesis.

CoA synthase is also of importance in this process. 4′-phosphopantetheine adenylyltransferase and dephospho CoA kinase activities are both catalyzed by CoA synthase [126]. The full-length CoA synthase is associated with the mitochondrial outer membrane, whereas the removal of the N-terminal region relocates the enzyme to the cytosol. Phosphatidylcholine and phosphatidylethanolamine, which are principle components of the mitochondrial outer membrane, are potent activators of both enzymatic activities of CoA synthase. Taken together, it may be inferred that CoA synthesis is regulated by phospholipids and intimately linked to mitochondrial function [118]. At steady state, cytosolic CoA concentrations range from 0.02 to 0.15 mM, mitochondrial concentrations range from 2 to 5 mM, and peroxisomal concentration are ~0.5 mM CoA [106,108].

Acyl Carrier Protein

ACP is also referred to as a ''macro-cofactor'' because in bacteria, yeast, and plants, it is composed of a dissociable polypeptide chain (MW ~8500–8700 Da) to which 4′-phosphopantetheine is attached [43,44,127]. 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 ACP, i.e., one of seven functional or catalytic domains on each of the two subunits that comprise fatty acid synthase (Table 9.3).

In addition to fatty acid production and catabolism, in yeast, bacteria, and plants, capable of essential amino acid synthesis, proteins with 4′-phosphopantetheine attachment sites are utilized. An example is aminoadipic acid reductase (e.g., LYS2 in yeast). The pantetheine transferase (LYS5), which aids in the activation of aminoadipic acid reductase, has also been isolated and cloned from a human source, i.e., a putative human homolog to the LYS5 gene [128].

Regarding ACP assembly to form holo-ACP, apo-ACP is posttranslationally modified via transfer of 4′-phosphopantetheine from CoA to a serine residue on apo-ACP [126,127,129]. The resulting holo-ACP is then active as the central coenzyme of fatty acid biosynthesis, either as individual subunit in bacterial systems or as a specific domain in the fatty acid synthetase complex in higher animals (Figure 9.4). Moreover, the transfer of the 4′-phosphopantetheine moiety of CoA to acyl carrier proteins may also serve as an alternate to CoA degradation or catabolism, i.e., ACP formation has the potential of providing an additional strategy for coordination of CoA levels [117,118,129].

In summary, the regulation of pantothenic acid kinase is complex and occurs via allosteric and transcriptional mechanisms. Multiple approaches to regulating this important enzyme are of obvious importance given the central roles and importance of both ACP and CoA to intermediary metabolism, protein processing, and gene regulation. In addition to the allosteric controls, transcriptional regulation by peroxisome proliferator activated receptor transcription factors, sterol regulatory element binding proteins (SREBP), and interaction with the glucose response element [95] are also essential.

TABLE 9.3
Catalytic Sites Associated with the Fatty Acid Synthase Complex

Catalytic Site	Function
Acetyl transferase	Catalyzes the transfer of an activated acetyl group on CoA to the sulfidryl group of 4′-phosphopantetheine (ACP domain). In the next 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 sulfhydryl group free for step 2
Malonyl transferase	Catalyzes the transfer of successive incoming malonyl groups to 4′-phosphopantetheine
3-Oxoacyl synthetase	Catalyzes the first condensation reaction in the process. The acetyl moiety (transferred in step 1) occurs with decarboxylation and condensation to yield a 3-oxobutryl (acetoacetyl) derivative. In the subsequent series of cycles, the newly formed acyl moieties react with the malonyl group added at each cycle (see step 6)
Oxoacyl reductase	Catalyzes reductions of acetoacetyl or 3-oxoacyl intermediates. The first cycle of this reaction generates D-hydroxybutyrate, and in subsequent cycles, hydroxyfatty acids
3-Hydroxyacyl dehydratase	Catalyzes the removal of a molecule of water from the 3-hydroxyacyl derivatives produced in step 4 to form enoyl derivatives
Enoyl reductase	Catalyzes the reduction of the enoyl derivatives (step 5). This acyl group is transferred to the sulfidryl 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 high-affinity substrate for the remaining enzyme of the complex, thioester hydrolase
Thioester hydrolase	This enzyme liberates palmitic acid (step 6) from the 4′-phosphopantetheine arm

SELECTED PHYSIOLOGIC FUNCTIONS OF ACP AND CoA

To reiterate, the functions of pantothenic acid as a vitamin are inexorably linked to processes that utilize CoA as a substrate and cosubstrate, particularly given that the bulk of 4′-phosphopantotheine incorporated into ACP also derives from transfer reactions that require CoA as substrate. Descriptions of the hundreds of reactions involving CoA in acetyl and acyl transfers are beyond the scope of a chapter specifically focused on pantothenic acid. However, the following descriptions (Table 9.4) were chosen to underscore how pantothenic acid as a component of CoA and ACP is central to virtually all aspects of metabolism.

CoA and ACP as High-Energy Intermediates

Intermediates arising from the transfer reactions catalyzed by CoA and 4′-phosphopantetheine in ACP are "high-energy" compounds [130]. Thioesters (–S–CO–R) are thermodynamically

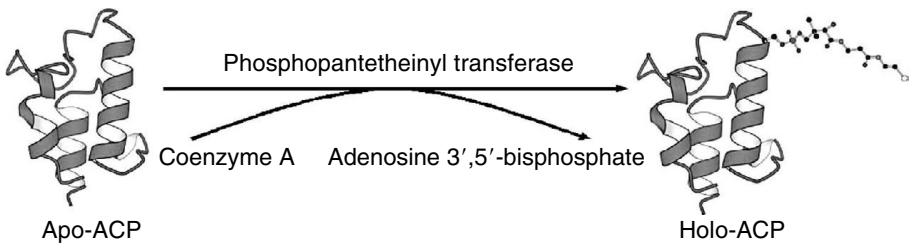
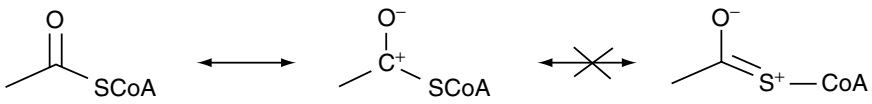


FIGURE 9.4 Pantethenylation of acyl carrier protein.

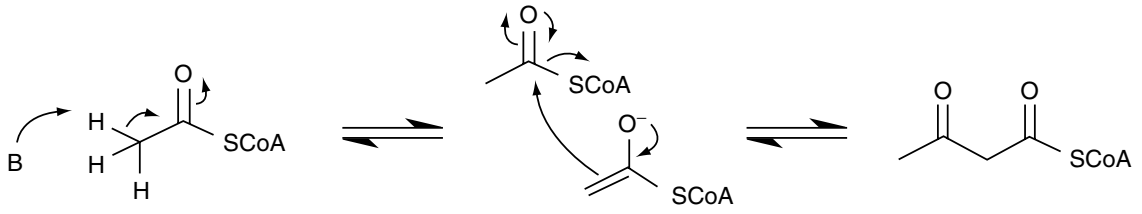
TABLE 9.4
Functions of CoA and ACP

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 transcriptional regulation, e.g., acetylation of histone
Protein acylation (e.g., myristic and palmitic acid, and prenyl moiety additions)	Compartmentalization and activation of hormones and transcription factors

less stable than typical esters (–O–CO–R) or amides (–N–CO–R). The double-bond character of the C═O bond in –S–C═O–R does not extend significantly into the C–S bond, i.e., in thiol esters the d-orbitals of sulfur do not overlap with the p-orbitals of carbon. This causes thioesters to have relatively high-energy potential, and for most reactions involving CoA or ACP, no additional energy, for example, from ATP hydrolysis, is required for transfer of the acetyl or acyl group. At pH 7.0, the $-\Delta G$ of hydrolysis is ~7.5 kcal for acetyl coenzyme A and 10.5 kcal for acetoacetyl CoA, compared with 7–8 kcal for the hydrolysis of adenosine triphosphate to AMP plus PP_i or ADP plus P_i. CoA or ACP also reacts with acetyl or acyl groups to form thioesters. The pK_a of the thiol in CoA–SH is ~10 (ROH ~ 16); at physiological pH, reasonable amounts of CoA–S– can be formed. CoA–SH is a potent nucleophile and more nucleophilic than RO–; moreover, RS– is a much better leaving group than RO–. Therefore, there is no mesomeric effect that makes the carbonyl group more polar than in regular ester [R–O–CO–R′] or amide bonds [R–N–CO–R′].



Their reactivity toward nucleophiles lies between esters and anhydrides. Thiol esters are easier to enolize than esters, i.e., the α-hydrogens are more acidic.



As such, acetyl CoA is involved in Claisen condensations, which is the basis of fatty acid, polyketide, phenol, terpene, and steroid biosynthesis. Coenzyme A is also central to the balance between carbohydrate metabolism and fat metabolism. Carbohydrate metabolism

needs some CoA for the citric acid cycle to continue, and fat metabolism needs a larger amount of CoA for breaking down fatty acid chains during β-oxidation [120].

Synthetic Versus Catabolic Processes Involving Pantetheine

As a fundamental distinction, CoA is involved in a broad array of acetyl and acyl transfer reactions and processes related to primarily oxidative metabolism and catabolism, whereas ACP is involved in synthetic reactions (Table 9.4). The adenosyl moiety of CoA provides a site for tight binding to CoA-requiring enzymes, while allowing the 4′-phosphopantetheine portion to serve as a flexible arm to move substrates from one catalytic center to another [43,120]. Similarly, when pantothenic acid (as 4′-phosphopantetheine) in ACP is used in transfer reactions, it also functions as a flexible arm that allows for an orderly and systematic presentation of thiol ester derivatives to each of the active centers of the FAS complex described in the previous section. A FAS system also exists in mitochondria [131]. The mitochondrial FAS pathway is novel in that it is similar to the FAS pathway in bacteria (designated the ''type ii'' pathway), for example, discrete soluble protein catalyzes each step of the reaction cycle rather than a multidomain complex.

Acetylations as Regulatory Signals

The addition of an acetyl group into an amino acid –[NH_2] or –[C═O–OH] function can markedly alter chemical properties. The same is true for biogenic amines, carbohydrates, complex lipids and hormones, xenobiotics, and drugs [132–137]. Specific compounds range from acetylcholine to melatonin to structural carbohydrates which are subject to O-linked acetylations. Examples include acetylated sialic acids (under the control of two groups of enzymes, *O*-acetyltransferases and 9-*O*-acetylesterases), cell surface antigens, and a wide variety of lipopolysaccharides, and *N*-acetylgangliosides. Acetylation is critical to cell–cell surface and cell surface protein–protein interactions (e.g., antigenic sites and determinants).

Of the hundreds of examples of covalently modified proteins, acetylation may be the most common [138,139]. Acetylations are catalyzed by a wide range of acetyltransferases that transfer acetyl groups from acetyl CoA to amino groups. Acetylation can alter enzymatic activity, stability, DNA binding, protein–protein/peptide interactions [140–145].

Amino-terminal acetylations occur cotranslationally and posttranslationally on processed eukaryotic regulatory peptides [140–150]. Proteins with serine and alanine termini are the most frequently acetylated, although methionine, glycine, and threonine may also be targets. This type of acetylation is usually irreversible and occurs shortly after the initiation of translation. The biological significance of amino-terminal modification varies in that some proteins require acetylation for function whereas others do not have an absolute requirement. In some cases, the process may be promiscuous, given the large number of proteins that may be acetylated. For example, it is estimated that over 50% of all proteins are acetylated [149].

Lysine residues are also target for acetylations [143]. Lysine acetylations also occur posttranslationally. Histones, transcription factors, cotranscriptional activators, nuclear receptors, and α-tubulin are proteins in which acetylation of specific lysyl residues modulates or alters function [147,148,150]. Acetylation occurs on internal lysine residues within these proteins, and is balanced by the action of a large number of deacetylases [141]. The deacetylases are NAD-dependent. Instead of water, the NAD-dependent deacetylases use a highly reactive ADP-ribose intermediate as a recipient for the acetyl group. The products of the reaction are nicotinamide, acetyl ADP-ribose, and a deacetylated substrate [145]. As an example of an important function, regions of chromatin that are inactive exist as hypo-acetylated heterochromatin-like (tightly packaged) domains. Therefore,

acetylation–deacetylation results in different states of chromatin configuration and is an important regulator of gene expression [145].

Other nonhistone proteins and transcription fractions that are reversibly acetylated have been implicated in protein–protein interactions and have been shown to facilitate specific binding of regulatory proteins, such as steroid hormone receptors or that modulate transcription by altering protein–protein interactions (e.g., high-mobility group proteins: HMG1 and HMG2). From a regulatory perspective, although there is no clear evidence that acetyltransferases act in classical cascade sequences (e.g., similar to phosphorylation or dephosphorylation signals), acetylations do alter the charge of the targeted lysyl group in a given protein. Such modifications can markedly influence or cause changes in protein structure.

Acylation Reactions

Another type of CoA facilitated posttranslational modification is acylation. Acylations occur by covalent attachment of lipid groups to change the polarity and strengthen the association of an acylated protein with membranes, both intra- and extracellularly. To date, the best characterized acylation pathways are those involving S-acyl linkages to proteins. Work with Ras proteins has shown that the S-acylation–deacylation cycle along with prenylation and carboxylmethylation may regulate the cycling of Ras between intracellular membrane compartments [151,152]. Indeed, many signaling proteins (e.g., receptors, G-proteins, protein tyrosine kinases, and other cell membrane "scaffolding" molecules) are acylated. Examples of acylations include S-acylation [153] (predominately the addition of a palmitoyl group), N-terminal myristoylations [109], and C-terminal prenylations and internal prenylations [154].

PANTOTHENIC ACID DEFICIENCY, CLINICAL RELATIONSHIPS, AND POTENTIAL INTERACTIONS INVOLVING POLYMORPHISMS

Pantothenic acid deficiency would be expected to result in generalized malaise, perturbations in CoA and lipid metabolism, and mitochondrial dysfunction. In turn, altered homeostasis of CoA would be expected to be associated with a number of disease states; indeed CoA has been described as a component of diabetes, alcoholism, and Reye syndrome [37,43]. Changes in or responses to hormones important to lipid metabolism (e.g., glucocorticoids, insulin, glucagon, and PPAR agonists, such as clofibrate) also occur with either pantothenic acid deficiency or in response to pantothenic acid kinase inhibitors. To reiterate, severe deficiencies of pantothenate are difficult to achieve (e.g., even commercial "vitamin-free" casein can contain up to 3 mg pantothenate/kg [155]). Nevertheless, under conditions of mild pantothenate deficiency in which weight differences between groups are not observed, serum triglyceride and free fatty acid levels are elevated, a reflection of reduced CoA levels.

In deficient states, pantothenate is reasonably conserved, particularly when there is prior exposure to the vitamin. For example, in studies using rodent embryos explanted at 9.0, 9.5, and 10.5 days and cultured for periods of 2 days or more in vitamin-free serum, some type of vitamin augmentation was necessary for normal growth [156]. However, lack of vitamins has a more marked effect on the younger embryos than on those explanted at 10.5 days. Experiments with media deficient in individual vitamins show that for normal development, 9.0 day embryos required a number of vitamins and biofactors (e.g., pantothenic acid, riboflavin, inositol, folic acid, and niacinamide); however, 10.5 day embryos need only riboflavin added to serum using growth and closure of the hindbrain as indices. In animals, the classical signs of deficiency include growth retardation and dermatitis as a secondary consequence of altered lipid metabolism [6,7,9,12,13,29,157–167]. Neurological, immunological [6,167], hematological, reproductive [29,162,168], and gastrointestinal pathologies

TABLE 9.5
Effects of Pantothenic Acid Deficiency in Selected Species

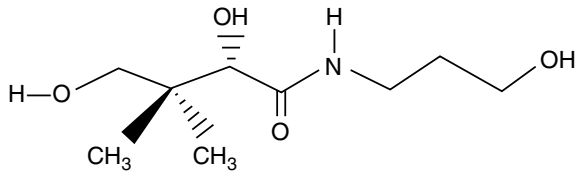
Species	Symptoms
Chicken	Dermatitis around beak, feet, and eyes; poor feathering; spinal cord myelin degeneration; involution of the thymus; fatty degeneration of the liver
Fish	Anorectic behavior; listlessness; fused gill lamellae; reproductive failure
Rat	Dermatitis; loss of hair color with alopecia; hemorrhagic necrosis of the adrenals; duodenal ulcer; spastic gait; anemia; leukopenia; impaired antibody production; gonadal atrophy with infertility
Dog	Anorexia; diarrhea; acute encephalopathy; coma; hypoglycemia; leukocytosis; hyperammonemia; hyperlactemia; hepatic steatosis; mitochondrial enlargement
Pig	Dermatitis; hair loss; diarrhea with impaired sodium, potassium, and glucose absorption; lachrymation; ulcerative colitis; spinal cord and peripheral nerve lesions with spastic gait

[169] have been reported. The effects of pantothenic acid deficiency in different species are summarized in Table 9.5.

What is known about pantothenic acid deficiency in humans comes primarily from two sources. 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, numbness and burning sensations were only reversed on pantothenic acid supplementation [170]. Second, experimental pantothenic acid deficiency has 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 [24,159,171–175]. Observed symptoms in humans also included numbness and burning of the hands and feet, as well as some of the other symptoms listed in Table 9.5. 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 [176].

With respect to temporal expression of pantothenic acid deficiency, if 5 mg or more is needed per day by humans, it may be predicted that with a severe deficiency of pantothenic acid, ~6 weeks would be required in an adult before clear signs of deficiency are observed. A daily loss of 4–6 mg of pantothenic acid represents a 1%–2% loss of the body pool of pantothenic acid in humans. For example, for many water-soluble vitamins (at a loss of 1%–2% of the body pool) 1–2 months of depletion results in deficiency signs [37,49]. In this regard, from the limited studies on pantothenic acid depletion ~6 weeks of severe depletion are required before urinary pantothenic acid decreases to a basal level of excretion [79,177,178].

With regard to clinical applications, claims for pantothenic acid range from prevention and treatment of graying hair (based on the observation that pantothenic acid deficiency in rodents causes fur to gray) to improved athletic performance. Several studies have indicated that pantetheine, in doses ranging from 500 to 1200 mg/day, may lower total serum cholesterol, low-density lipoprotein cholesterol, and triacylglycerols [25,179–189]. Oral administration of pantothenic acid and application of pantothenol ointment to the skin seems to accelerate the closure of skin wounds and increase the strength of scar tissue in animal models [190–192].



Structure of pantothenol

However, the results are equivocal in humans. In a randomized, double-blind study examining the effect of supplementing patients undergoing surgery for tattoo removal with pantothenic acid did not demonstrate any significant improvement in the wound-healing process [191]. Papers may also be found on lupus erythematosus and pantothenic acid deficiency. Procainamide, hydralazine, and isoniazid are known to cause drug-induced lupus erythematosus. Because these drugs are metabolized via CoA-dependent acetylation, it is argued that there is an increased demand for CoA, which causes a pantothenic acid deficit. However, clinical trials involving pantothenic acid supplementation and given diseases, lupus in particular, have yet to show promise [193–199].

Polymorphisms or gene defects in enzymes involved in CoA synthesis pathway exist, and result in disease states, such as Hallervorden–Spatz syndrome or pantothenate kinase–associated neurodegeneration [89,91,96,113–115]. This disease results from mutations in PanK2, which is the most abundantly expressed form in the brain and localized in mitochondria. This autosomal recessive neurodegenerative disorder is characterized clinically by dystonia and optic atrophy or pigmentary retinopathy with iron deposits in the basal ganglia and globus pallidus [114,115].

PHARMACOLOGY

Several pantothenate-related compounds have been recommended as inhibitors of *Staphylococcus aureus* infections or proliferation of malarial parasites. Most of these analogs retain the 2,4-dihydroxy-3,3-dimethylbutyramide core of pantothenic acid. Many analogs are relatively specific, inhibiting the proliferation of human cells only at concentrations several fold higher than those required for inhibition of parasite or bacterial growth. The structures and chemical characteristics of selected analogs are provided in Figure 9.5.

Some classic observations utilizing pantothenic acid antagonists such as ω-methyl-pantothenic acid and calcium hopantenate were mentioned in the previous section. Tragic lessons were learned utilizing these compounds. In moderate doses, ω-methyl-pantothenic acid can be potentially lethal [24]. Similarly, calcium hopantenate administration may cause fatal and acute encephalopathy ([176]).

As was noted in the previous section, pantothenic acid supplementation has also been associated with lipid-lowering effects, but pantothenic acid administration does not compete with the excellent drugs that are currently available, although it is conceivable that the

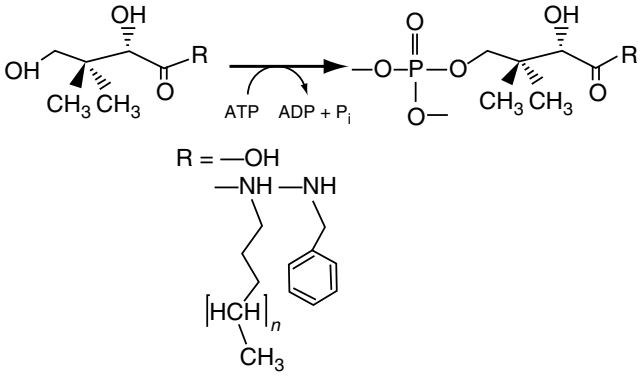


FIGURE 9.5 Pantothenic acid analogs that have potential as CoA synthesis inhibitors. Modifying the carboxyl moiety of pantothenic acid by the addition of an aromatic or acyl group in amide linkage results in a derivative that is effective as an inhibitor of 4′-phosphopantothenoylcysteine synthetase and subsequent transferases (see Figure 9.2).

combination of pantetheine and an appropriate peroxisomal activated regulator receptor agonists or coactivator may be of utility in normalizing lipid metabolism [95,179].

Regarding other applications, amelioration of the adverse effects of valproic acid on ketogenesis and liver CoA metabolism by cotreatment with pantothenate and carnitine has proven successful in developing mice. Valproic acid (CH_3–CH_2–CH_2]$_2$=CH–COOH) is a Food and Drug Administration (FDA)-approved drug used in the treatment of epilepsy and has been used in the treatment of manic episodes associated with bipolar disorder. Considering the side effects of valproic acid (nausea, tremors, and liver failure), pantothenic acid supplementation has been suggested to have some promise in modulating such symptoms when valproic acid is the drug chosen [200–205].

TOXICITY

Pantothenic acid is generally safe, even at extremely high doses. Excesses are mostly excreted in the urine. Very high oral doses (>1 g/day) of pantothenic acid may be associated with diarrhea and gastrointestinal disturbances. However, there are no reports of acute toxic effects in humans, or commonly available pharmaceutical forms of pantothenic acid, other than gastrointestinal disturbance. Indeed, no data are available that suggest neurotoxicity, carcinogenicity, genotoxicity, or reproductive toxicity. Calcium pantothenate, sodium pantothenate, and panthenol are not mutagenic in bacterial tests.

In animals, young rats fed 50 mg/day (~0.5 g/kg bw/day) as calcium pantothenate for 190 days had no adverse effects. When bred, their offspring were maintained using the same diets with no signs of abnormal growth or gross pathology. Similar studies in mice (both oral and i.p.) have led to the same conclusions. In the early 1940s, Unna and Greslin [15,18] reported acute and chronic toxicity tests with D-calcium pantothenate in mice, rats, dogs, and monkeys. Acute oral LD_{50} values were 10,000 mg/kg bw, mice, and rats, with lethal doses producing death by respiratory failure. An oral dose of 1000 mg/kg bw produced no toxic signs in dogs or in one monkey. Oral dosing (500 or 2000 mg/kg bw/day to rats, 50 mg/kg bw/day to dogs, 200–250 mg/kg bw/day to monkeys) for 6 months produced no toxic signs, weight loss, or evidence of histopathological changes at autopsy [206].

In humans, Welsh [193,195] reported that giving patients high doses of pantothenic acid derivatives ($\leq$10–15 g) with the goal of treating symptoms of lupus erythematosus (see previous section) had no side effects other than transient nausea and gastric distress. Likewise, Goldman [207] described the use of panthenol for the treatment of lupus erythematosus at various dosage levels up to 8–10 g/day, for periods ranging from 5 days to 6 months with few side effects. Webster [70] carried out a randomized, double-blind, placebo-controlled, crossover study to assess the effects of pantothenic acid on exercise performance in six highly trained cyclists. For each subject, two testing (cycling performance) sessions were carried out, separated by a 21 day washout period. One testing session was carried out immediately after 7 days supplementation with pantotheine derivatives at ~2 g/day or placebo. No significant differences were identified between assessed parameters of cycling performance and no side effects of the therapy were reported. In summary, high doses of pantothenic acid, 100–500 times the normal requirements, appear well tolerated.

STATUS DETERMINATION

Whole blood concentration and urinary excretion reflects pantothenic acid status. In humans, whole blood concentrations typically range from 1.6 to 2.7 μmol/L [37,47,85,208] 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 [79]. 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.

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 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 [52,53,84,85,209,210].

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