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Pantothenic Acid

11.1 Background

The biological activity of pantothenic acid is attributable to its incorporation into the molecular structures of coenzyme A and acyl carrier protein. As a component of coenzyme A, pantothenic acid is essential for numerous reactions involved in the release of energy from carbohydrates, fats, and amino acids. In carbohydrate metabolism, the formation of acetyl-coenzyme A is necessary for introducing acyl groups into the tricarboxylic acid cycle. Other roles of acetyl-coenzyme A include its requirement for the acetylation of amino sugars, which are constituents of various mucopolysaccharides of connective tissues, and also for the acetylation of choline to form the neurotransmitter acetylcholine. Succinyl-coenzyme A is a precursor for porphyrin and hence for hemoglobin and cytochromes. Acyl carrier protein plays a major role in the biosynthesis of fatty acids.

Because of the widespread distribution of pantothenic acid in foods, a dietary deficiency of the vitamin is virtually impossible, apart from circumstances of severe malnutrition. When volunteers were fed a metabolic antagonist, omega-methylpantothenic acid, along with a diet low in pantothenic acid, the most persistent of the many symptoms were fatigue, headache, and the sensation of weakness. Reported neurological manifestations include numbness and "burning feet" syndrome.

Pantothenic acid has very low toxicity; even with oral amounts as high as 10–20 g of the calcium salt, the only reported problem was occasional diarrhea.

11.2 Chemical Structure, Biopotency, and Physicochemical Properties

11.2.1 Structure and Potency

Structures of pantothenic acid and compounds containing a pantothenate moiety are shown in Figure 11.1. Pantothenic acid ($C_9H_{17}O_5N$,

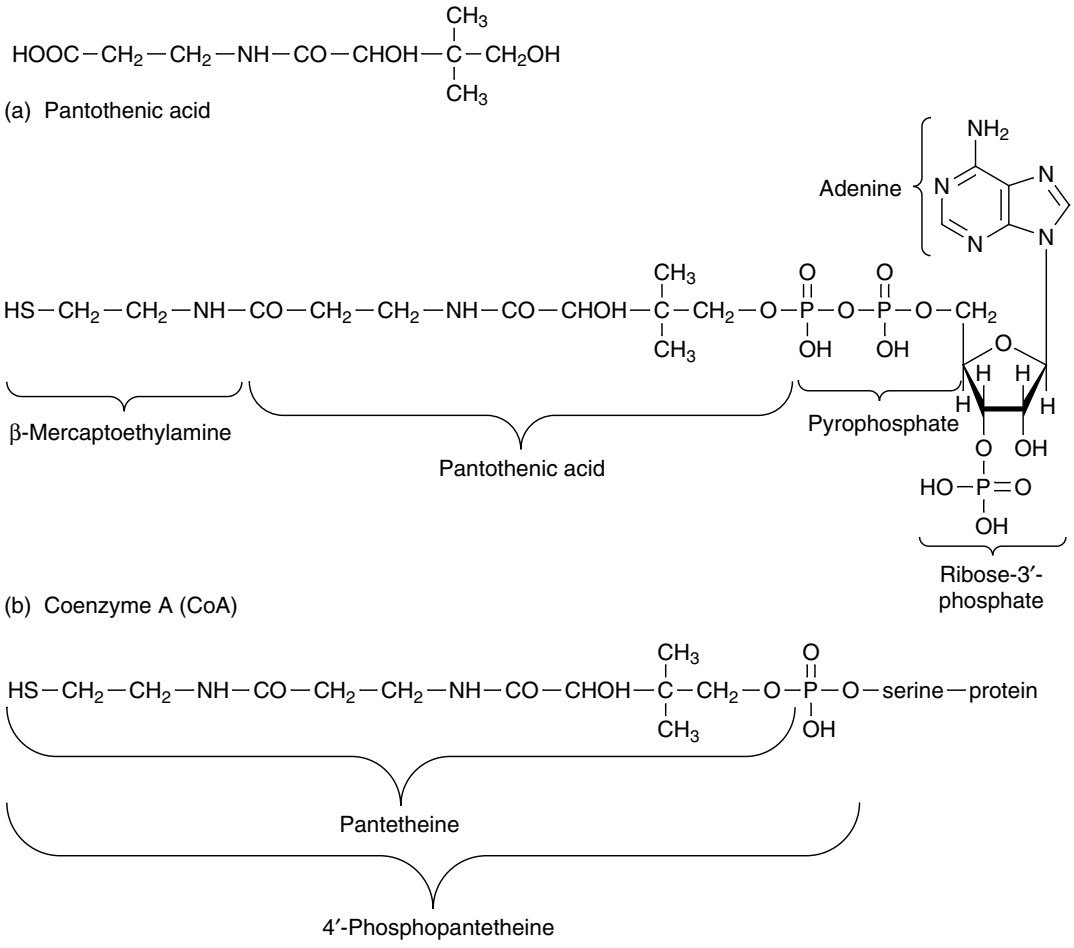

FIGURE 11.1
Structures of (a) pantothenic acid, (b) coenzyme A, and (c) acyl carrier protein.

MW = 219.2) comprises a derivative of butyric acid (pantoic acid) joined by a peptide linkage to the amino acid β-alanine. The molecule is optically active but only the D(+)-enantiomorph occurs in nature. Synthetic pantothenic acid is a racemic mixture and, because only the D isomer is biologically active, this fact must be considered if the DL mixture is to be used therapeutically. Pantothenic acid is a pale yellow oil which is extremely hygroscopic, and so is unsuitable for commercial application. For human food supplements, calcium D-pantothenate [$(C_9H_{16}O_5N)_2Ca$, MW = 476.5] is used.

11.2.2 Physicochemical Properties

11.2.2.1 Appearance and Solubility

Calcium pantothenate is a colorless, odorless, bitter-tasting, moderately hygroscopic, microcrystalline powder which decomposes at ca. 200°C.

The pH of an aqueous 5% (w/v) solution of calcium pantothenate is 7.2–8.0; the pK_a value is 4.4 (dissociation of the carbonyl group). Pantothenic acid is readily soluble in water and ethyl acetate and slightly soluble in diethyl ether; the calcium salt is more soluble in water (40 g/100 ml), only slightly soluble in ethyl acetate, and insoluble in diethyl ether.

11.2.2.2 Stability in Aqueous Solution

The stability of pantothenic acid and its calcium salt in aqueous solution is highly dependent on the pH. In contrast to other B-vitamins, pantothenic acid becomes more stable as the pH of the solution increases. Solutions of calcium pantothenate are most stable between pH 5 and 7 but, even so, are not stable to autoclaving, and therefore sterilization by ultrafiltration is necessary. Below and above these pH values, solutions of calcium pantothenate are thermolabile. Alkaline hydrolysis yields pantoic acid and β-alanine, whereas acid hydrolysis yields the gamma-lactone of pantoic acid [1]. Pantothenic acid is unaffected by atmospheric oxygen and light.

11.3 Pantothenic Acid in Foods

11.3.1 Occurrence

Pantothenic acid is widely distributed in foods of animal and plant origin. The vitamin is particularly abundant in liver, kidney, yeast, egg yolk, and broccoli, which contain more than 50 μg pantothenate/g dry weight. Exceptionally high levels are found in royal jelly (511 μg/g) and in ovaries of tuna and cod (2.32 mg/g) [2].

Pantothenic acid exists in foodstuffs in its free form, as well as bound in coenzyme A and acyl carrier protein. Pakin et al. [3] used selective enzymes and HPLC analysis to determine free and bound pantothenic acid in various foods (Table 11.1). Free pantothenic acid was found in all foods analyzed. Coenzyme A was the major form of the vitamin in yeast, pig liver, and peas, but this compound was not significantly present in avocado, carrots, French beans, or salmon. Several foods of both animal and plant origin contained significant amounts of bound pantothenic acid other than coenzyme A.

11.3.2 Stability

Pantothenic acid has good stability in most foods during processing, but is susceptible to leaching in the blanching of vegetables and home cooking. The vitamin content was higher in peas cooked in steam as

TABLE 11.1

Contents of Free and Bound Pantothenic Acid in Various Foods

	Concentration (μg/g)[a]		
Food	**Free PA**	**PA Free and Bound in Coenzyme A**	**Total PA**
Avocado	8.2 (0.2)[b]	8.4 (0.2)[b,c]	8.9 (0.3)[c]
Carrot	3.45 (0.05)[b]	3.6 (0.2)[b,c]	3.9 (0.3)[c]
French beans	1.8 (0.2)[b]	2.0 (0.2)[b]	2.5 (0.2)
Lentils	10.6 (0.4)	14.7 (0.4)	17.7 (0.3)
Peas	2.0 (0.2)	4.4 (0.2)	5.0 (0.2)
Spinach	0.80 (0.08)	1.10 (0.09)[c]	1.13 (0.03)[c]
Chicken meat	10.2 (0.2)	13.0 (0.1)	15.1 (0.8)
Pig liver	30.7 (0.1)	63 (2)	73 (2)
Salmon	11.2 (0.05)[b]	11.9 (0.4)[b]	15.3 (0.7)
Chicken egg	17.8 (0.2)	22.3 (0.5)[c]	23.0 (0.5)[c]
Powdered milk (fortified)	46.3 (0.7)	54 (2)	57.1 (0.9)
Yeast	24.1 (0.7)	73 (3)	80 (3)

Note: PA, pantothenic acid.

[a]Average of three determinations (standard deviation in parentheses).

[b,c]Not significantly different ($P > 0.05$) when the means of two samples are compared.

Source: From Pakin, C., Bergaetzlé, M., Hubscher, V., Aoudé-Werner, D., and Hasselmann, C., *J. Chromatogr. A*, 1035, 87, 2004. With permission from Elsevier.

compared with boiling [4]. Water blanching incurred more loss of pantothenic acid than steam blanching for spinach and broccoli. Free pantothenic acid was lost to greater extent than total pantothenic acid during water blanching of both vegetables [5]. Hoppner and Lampi [6] investigated the effect of pre-soaking procedures and cooking times on the retention of pantothenic acid (and also biotin) in 25 different dried legumes. Before cooking for 20, 90, or 150 min, pooled samples of each legume were subjected to either a short soak or a long soak. For the short soak, one volume of the legume in three volumes of water was brought to boil and boiled for 2 min, covered, and left to soak for 1 h while cooling to room temperature. For the long soak, one volume of the legume in three volumes of water was left to soak overnight (16 h) at room temperature. Legumes in the 20-min cooking category were also prepared without pre-soak. After cooking, samples were weighed, freeze-dried, finely ground, and analyzed for pantothenic acid content by microbiological assay. Legumes cooked for 20 min without pre-soaking retained more pantothenic acid than those subjected to pre-soaking. When pre-soaked, most of the legumes in the 20- and 90-min cooking group retained more pantothenic acid after the long soak than after the short soak with boiling.

This was true in only half the legumes in the 150-min cooking group. As shown in Table 11.2, average retentions for pantothenic acid in the long-soaked legumes were higher ($P < 0.05$) than those in the short-soaked legumes for the 20- and 90-min cooking times. There was no significant difference ($P > 0.05$) between the two pre-soaking treatments for legumes cooked for 150 min. The more severe short soak with boiling prior to cooking for 20 or 90 min probably liberated bound pantothenic acid, thereby increasing leaching of free vitamin into the soak water.

Retention of pantothenic acid in oven-roasted beef loin averaged 89%, with an average recovery in the drip of 19%. By comparison, average retention in oven-braised beef was 56%, with 44% recovered in the drip. Thus approximately twice as much pantothenic acid was transferred to the drip by braising as by roasting [7]. There is no appreciable loss of pantothenic acid during frozen storage of meat [8].

In an evaluation of data compiled by Orr [9], Schroeder [10] reported that the canning and freezing of foods incurs large losses of pantothenic acid. In canned foods of animal origin, losses ranged from 20 to 35%, and in canned vegetable foods from 46 to 78%. Freezing losses in animal foods ranged from 21 to 70%, and in vegetable foods from 37 to 57%. Grains lost 37–74% of the original pantothenic acid content during conversion to various cereal products, and meats lost 50–75% during conversion to comminuted products. Later studies [11] have also indicated large losses of pantothenic acid in many highly processed foods, including products made from refined grains, fruit products, and fat- or cereal-extended meats and fish. When stored at room temperature ($22 \pm 2^{\circ}C$), canned Dutch Army meals (consisting of meat, vegetables, pulses, and potatoes) lost approximately 50% of their pantothenic acid

TABLE 11.2

Effect of Pre-Soak Methods on the Mean Pantothenic Acid Retention in Dried Legumes After Cooking[a]

Cooking Time (min)	No Pre-Soak (%)	Short-Soak (%)	Long-Soak (%)	Statistical Difference
20	75.8 ± 15.0	—	—	
20		33.0 ± 6.6	43.8 ± 9.0	*
90		40.2 ± 7.7	58.1 ± 13.9	*
150		50.8 ± 14.6	55.1 ± 18.4	ns

Note: *Significant ($P < 0.05$); ns, not significant ($P > 0.05$).

[a]Values were derived from analysis of 25 different legumes.

Source: From Hoppner, K. and Lampi, B., Pantothenic acid and biotin retention in cooked legumes, *J. Food Sci.*, 58, 1084, 1993. With permission.

in 5 years of storage [12]. Losses of pantothenic acid during milk pasteurization, sterilization, and drying are usually less than 10% [13].

11.3.3 Applicability of Analytical Techniques

Pantothenic acid is routinely determined by microbiological assay. Gas chromatographic determination of the pantoyl lactone formed from pantothenic acid by acid hydrolysis has been applied to foodstuffs. HPLC methods have also been reported. Biospecific methods of analysis include the radioimmunoassay and the enzyme-linked immunosorbent assay (ELISA).

No international unit of pantothenic activity has been defined. Analytical results are generally expressed in weight units (mg) of pantothenic acid, using calcium pantothenate as the standard material: 1 mg of pantothenic acid is equivalent to 1.087 mg of calcium pantothenate.

11.4 Intestinal Absorption

The following discussion of absorption is taken from a more detailed account in a book by Ball [14] published in 2004.

Humans and other mammals cannot synthesize pantothenic acid and therefore they rely on dietary sources of the vitamin. Pantothenic acid is synthesized by the normal microflora in the large intestine, but the quantitative contribution of this endogenous vitamin to the host tissues is unknown.

11.4.1 Digestion and Absorption of Dietary Pantothenic Acid

Ingested coenzyme A is hydrolyzed in the intestinal lumen to pantetheine by the nonspecific action of pyrophosphatases and phosphatase. Pantetheine is then split into pantothenic acid and β-mercaptoethylamine by the action of pantotheinase secreted from the intestinal mucosa into the lumen [15]. Within the alkaline medium of the intestinal chyme, the vitamin exists primarily as the pantothenate anion.

Absorption of the free pantothenic acid takes place mainly in the jejunum. A so-called sodium-dependent multivitamin transporter (SMVT), which mediates placental and intestinal uptake of pantothenate, biotin, certain biotin analogs, and the essential metabolite lipoate, has been cloned from rat [16] and human [17] placenta and from rabbit intestine [18]. The functional characteristics of the cloned transporter are

similar to those observed in native intestinal membranes regarding substrate specificity, kinetics, and inhibitor profiles [19]. The transporter appears to interact primarily, though not exclusively, with the long side-chain of the substrate containing the carboxylate group, which is present in pantothenate, biotin, and lipoate. Messenger RNA transcripts of SMTV were shown to be present in all the tissues that were tested (intestine, liver, kidney, heart, lung, skeletal muscle, brain, and placenta), suggesting that this carrier protein may be involved in the uptake of pantothenate, biotin, and lipoate by all cell types [16]. The stoichiometry of the Na^+: vitamin cotransport appears to be 2:1, indicating an electrogenic transport process. Thus, both the Na^+ concentration gradient and the potential difference across the brush-border membrane drive the transport process.

Unlike other water-soluble vitamins which are absorbed by specific carrier-mediated mechanisms (ascorbic acid, biotin, and thiamin), the absorption of pantothenic acid is not adaptively regulated by its level of dietary intake [20]. Clear-cut pantothenic acid deficiency symptoms in humans are rarely found in practice and the vitamin is nontoxic at high doses. These factors could explain why a regulated absorption mechanism has not evolved for pantothenic acid.

11.4.2 Absorption of Bacterially Synthesized Pantothenic Acid in the Large Intestine

The normal microflora of the large intestine synthesizes pantothenic acid, but it is not known how much, if any, of this endogenous vitamin is available to the host tissues. In human subjects, absorption of pantothenic acid takes place equally well whether the vitamin is given orally or instilled directly into the lumen of the mid-transverse colon [21]. Said et al. [22] showed that human colonic NCM460 cells took up pantothenic acid by a Na^+-dependent, carrier-mediated process that was shared by biotin.

11.5 Bioavailability

Little information is at hand regarding the nutritional availability to the human of pantothenic acid in food commodities. Based on the urinary excretion of pantothenic acid, the availability for male human subjects ingesting the "average American diet" ranged from 40 to 61% with a mean of 50% [23]. Roth-Maier et al. [24] determined the prececal digestibility of endogenous pantothenic acid in five different foods using pigs subjected to an end-to-end ileo-rectal anastomosis. The foods

selected were wheat, coarse wholemeal bread, steamed potatoes, boiled pork, and boiled beef. These test foods were mixed with basal ingredients to provide edible meals, and to supply a minimum of pantothenic acid. All diets were fortified with minerals and fat-soluble vitamins, and the wheat, bread, and potato meals were additionally enriched with soybean oil and amino acids. The digestibilities of pantothenic acid from the wheat, potato, and meat meals ranged between 65 and 81% and were not statistically different from one another. The digestibility of pantothenic acid from the coarse wholemeal bread diet reached a level of only 28%.

References

1. Tannenbaum, S.R., Young, V.R., and Archer, M.C., Vitamins and minerals, in *Food Chemistry*, Fennema, O.R., Ed., 2nd ed., Marcel Dekker, New York, 1985, p. 477.
2. Plesovsky-Vig, N., Pantothenic acid, in *Modern Nutrition in Health and Disease*, 9th ed., Shils, M.E., Olson, J.A., Shike, M., and Ross, A.C., Eds., Lippincott Williams and Wilkins, Philadelphia, 1999, p. 423.
3. Pakin, C., Bergaentzlé, M., Hubscher, V., Aoudé-Werner, D., and Hasselmann, C., Fluorimetric determination of pantothenic acid in foods by liquid chromatography with post-column derivatization, *J. Chromatogr. A*, 1035, 87, 2004.
4. Kilgore, S.M. and Sistrunk, W.A., Effects of soaking treatments and cooking upon selected B-vitamins and the quality of blackeyed peas, *J. Food Sci.*, 46, 909, 1981.
5. Cheng, T.S. and Eitenmiller, R.R., Effects of processing and storage on the pantothenic acid content of spinach and broccoli, *J. Food Process. Preserv.*, 12, 115, 1988.
6. Hoppner, K. and Lampi, B., Pantothenic acid and biotin retention in cooked legumes. *J. Food Sci.*, 58, 1084, 1993.
7. Meyer, B.H., Mysinger, M.A., and Wodarski, L.A., Pantothenic acid and vitamin B_6 in beef, *J. Am. Diet. Assoc.*, 54, 122–125, 1969.
8. Engler, P.P. and Bowers, J.A., B-vitamin retention in meat during storage and preparation, *J. Am. Diet. Assoc.*, 69, 253, 1976.
9. Orr, M.L., Pantothenic acid, vitamin B_6 and vitamin B_{12} in foods, Home Economics Research Report No. 36, United States Department of Agriculture, Washington, DC, 1969.
10. Schroeder, H.A., Losses of vitamins and trace minerals resulting from processing and preservation of foods, *Am. J. Clin. Nutr.*, 24, 562, 1971.
11. Walsh, J.H., Wyse, B.W., and Hansen, R.G., Pantothenic acid content of 75 processed and cooked foods, *J. Am. Diet. Assoc.*, 78, 140, 1981.
12. Hellendoorn, E.W., de Groot, A.P., van der Mijlldekker, L.P., Slump, P., and Willems, J.J.L., Nutritive value of canned meals, *J. Am. Diet. Assoc.*, 58, 434, 1971.

13. Archer, M.C. and Tannenbaum, S.R., Vitamins, in *Nutritional and Safety Aspects of Food Processing*, Tannenbaum, S.R., Ed., Marcel Dekker, New York, 1979, p. 47.
14. Ball, G.F.M., *Vitamins: Their Role in the Human Body*, Blackwell Publishing Ltd., Oxford, 2004, p. 326.
15. Shibata, K., Gross, C.J., and Henderson, L.M., Hydrolysis and absorption of pantothenic acid and its coenzymes in the rat small intestine, *J. Nutr.*, 113, 2107, 1983.
16. Prasad, P.D., Wang, H., Kekuda, R., Fujita, T., Fei, Y.-J., Devoe, L.D., Leibach, F.H., and Ganapathy, V., Cloning and functional expression of a cDNA encoding a mammalian sodium-dependent vitamin transporter mediating the uptake of pantothenate, biotin, and lipoate, *J. Biol. Chem.*, 273 (13), 7501, 1998.
17. Wang, H., Huang, W., Fei, Y.-J., Xia, H., Yang-Feng, T.L., Leibach, F.H., Devoe, L.D., Ganapathy, V., and Prasad, P.D., Human placental Na^+-dependent multivitamin transporter: cloning, functional expression, gene structure, and chromosomal localization, *J. Biol. Chem.*, 274 (21), 14875, 1999.
18. Prasad, P.D., Wang, H., Huang, W., Fei, Y.-J., Leibach, F.H., Devoe, L.D., and Ganapathy, V., Molecular and functional characterization of the intestinal Na^+-dependent multivitamin transporter, *Arch. Biochem. Biophys.*, 366, 95, 1999.
19. Chatterjee, N.S., Kumar, C.K., Ortiz, A., Rubin, S.A., and Said, H.M., Molecular mechanism of the intestinal biotin transport process, *Am. J. Physiol.*, 277, C605, 1999.
20. Stein, E.D. and Diamond, J.M., Do dietary levels of pantothenic acid regulate its intestinal uptake in mice? *J. Nutr.*, 119, 1973, 1989.
21. Sorrell, M.F., Frank, O., Thomson, A.D., Aquino, H., and Baker, H., Absorption of vitamins from the large intestine *in vivo, Nutr. Rep. Int.*, 3, 143, 1971.
22. Said, H.M., Ortiz, A., McCloud, E., Dyer, D., Moyer, M.P., and Rubin, S., Biotin uptake by human colonic epithelial NCM460 cells: a carrier-mediated process shared with pantothenic acid, *Am. J. Physiol.*, 275, C1365, 1998.
23. Tarr, J.B., Tamura, T., and Stokstad, E.L.R., Availability of vitamin B_6 and pantothenate in an average American diet in man, *Am. J. Clin. Nutr.*, 34, 1328, 1981.
24. Roth-Maier, D.A., Wauer, A., Stangl, GI., and Kirchgessner, M., Precaecal digestibility of niacin and pantothenic acid from different foods, *Int. J. Vitam. Nutr. Res.*, 70, 8, 2000.