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Review

Comparative nutrition of pantothenic acid

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Pantothenic acid, a B-vitamin, is essential for all mammalian species that have been studied: humans, calves, pigs, dogs, rodents, and cats, as well as for poultry and fish. The different species develop various deficiency signs such as growth retardation; anorexia; changes in hair, feather, or skin; locomotor abnormalities; gastrointestinal problems; compromised immunofunctions; impaired adrenal functions; altered lipid and carbohydrate metabolism; and adverse breeding outcome. Because there are no reliable and sensitive criteria for assessing pantothenate status, the dietary requirements of different species are most frequently set at the level that results in maximum growth. The pantothenate requirement varies widely among different species and strains, and depends on the age, growth rate, and breeding stages of the animals. This review summarizes the deficiency signs and the requirements for pantothenate of different species, and discusses various factors that affect pantothenate requirements of the animals. (J. Nutr. Biochem. 7:312–321, 1996.)

Keywords: pantothenic acid; animal nutrition

Introduction

Coenzyme A (CoA), the principal coenzyme form of pantothenate in the cell, forms a thioester bond with acyl carbons, and thus mediates acyl transfer reactions in over 70 enzymatic pathways.[1] CoAs are found in the diverse pathways of fatty acid oxidation, cholesterol synthesis, heme synthesis, amino acid catabolism, acetylcholine synthesis, etc. (*Figure 1*). Phosphopantetheine, another coenzyme form of pantothenate, functions in mammalian cells principally as a part of fatty acid synthase.

Pantothenate was first recognized as a growth factor for yeast in 1933,[2] and as a "filtrate factor" and "chick antidermatitis factor" in 1939.[3,4] The B-vitamin was soon after isolated and synthesized.[5,6] In 1947, Lipmann and coworkers proved that pantothenate was a part of CoA.[7]

D-Pantothenate is converted to CoA through a five-enzyme sequence that begins with the phosphorylation of pantothenate by pantothenate kinase, and requires cysteine and four ATPs. The synthetic process was initially proposed by Brown[8] and established by Abiko and co-workers (*Figure 2*). Because CoA cannot pass through the plasma membrane,[9] the coenzyme must be synthesized in every cell.

The degradative pathway of CoA is similar, but not identical to the reversed synthetic route.[1] Degradation of CoA to pantetheine involves the nonspecific actions of lysosomal acid phosphatase,[10] and a non-specific nucleotide pyrophosphatase.[11] Pantetheine is then degraded to pantothenic acid and cysteamine by a specific amidase, pantetheinase, which was first characterized by Dupre and coworkers.[12] CoA is also dissimilated by the transfer of the 4′-phosphopantetheine portion to fatty acid synthase.[13]

Pantothenate, pantetheine, and CoA are all present in foods and can be used as sources of pantothenate. The absorption, uptake, and excretion mechanisms do not seem to differ among species. Pantothenate at low concentrations in the lumen is absorbed by a specific Na-dependent active transport mechanism,[14] whereas at high concentrations it is absorbed by a simple diffusion.[15] Pantetheine is absorbed from the intestine somewhat more rapidly than pantothenate, and a portion is hydrolyzed to pantothenate during passage.[16,17] Because pantetheine can also be phosphorylated by pantothenate kinase,[18] hydrolysis of pantetheine to pantothenate before conversion to CoA is unnecessary. In

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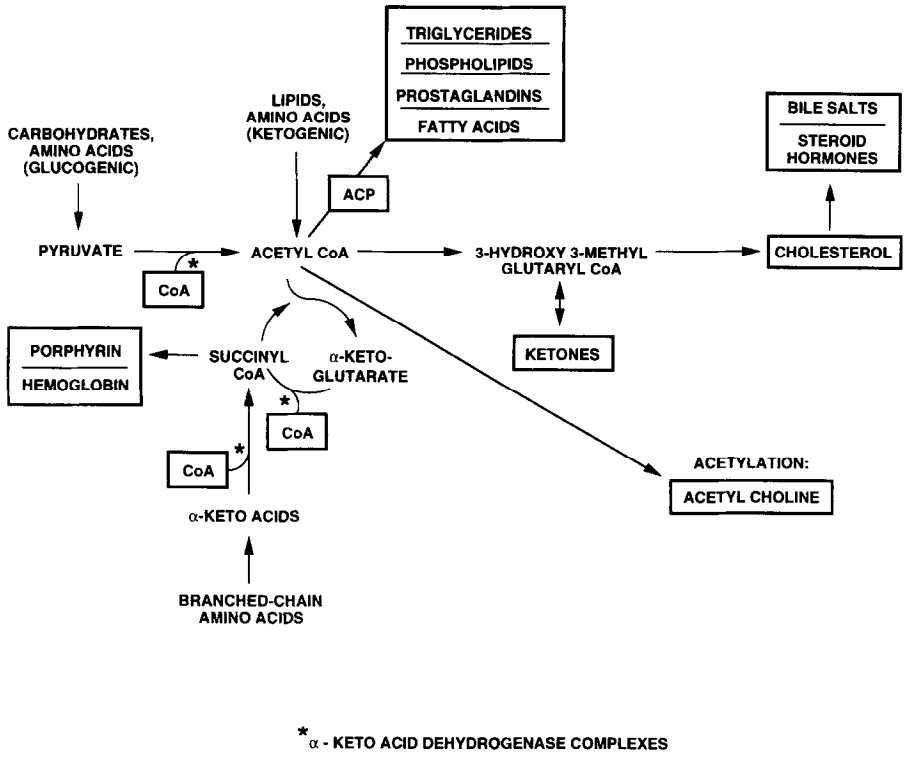

Figure 1 Biochemical pathways in which CoA and acyl carrier protein are essential. *alpha-ketoacid dehydrogenase complexes. Synthesis of compounds in the boxes require pantothenate coenzymes.[133]

the chick assay, the growth promotion effect of orally administered molar equivalent pantothenate, pantetheine, and CoA was 1.0, 0.9. and 0.61, respectively.[19–22]

A well-accepted, specific, and sensitive biochemical test to assess pantothenate nutritional status has been lacking. In establishing dietary requirements for pantothenate, researchers have frequently used maximal growth of disappearance of deficiency signs. This review summarizes 1) pantothenate deficiency signs reported in many species, 2) pantothenate requirements of different species, especially for growth and breeding, and 3) various factors that affect pantothenate requirements. Special attention was given in this review to the differences among the studies with possible reasons for the variation.

Pantothenate deficiency signs reported

Animals and fish show a wide range of signs when dietary pantothenate is deficient for varying durations: reduced growth rate, and decreased food intake and feed conversion efficiency leading to emaciation, dehydration, and sudden death; lesions of skin and changes in hair coat; bloody whiskers with porphyrin from the Harderian gland; disorders of the nervous system; myelin degeneration of spinal cord and peripheral nerves leading to paralysis and muscular incoordination and convulsion; gastrointestinal disorders such as stomach and intestinal ulceration, diarrhea, and colitis; compromised immunofunctions; impaired adrenal functions such as altered synthesis of corticosterone, and hemorrhagic necrosis of the cortex; alteration in lipid and carbohydrate metabolism; alteration in the reproductive system; alteration in blood formation. The uniform but non-specific signs of pantothenate deficiency observed in the young and growing members of almost all species are anorexia and decreased weight gain. Other specific deficiency signs seen in representative species are shown in *Table 1*.

Pantothenate deficiency has been induced in humans in 4 to 9 weeks by use of a pantothenate-deficient diet supplemented with omega-methyl pantothenate, a metabolic antagonist.[23–25] The antagonist hastened development and severity of pantothenate deficiency symptoms that resemble the deficiency signs observed in experimental animals: depression, personality changes, cardiac instability, frequent infection, fatique, abdominal pains, sleep disturbances, and neurological disorders such as numbness, paresthesis (abnormal sensation such as "burning feet" syndrome), muscle weakness, and cramps. Reye-like syndrome has also been reported in patients who use another metabolic antagonist, pantoyl-gamma butyric acid (also called pantoyl-GABA, or hopantothenate) for treating cognate and memory impairments in pathological states such as Alzheimer's disease.[26–28]

The pantothenate-deficiency signs observed in chicks led to the recognition of the compound as a growth factor and as a vitamin. The outwardly visible signs include decreased food intake; decreased weight gain; dermatitis at the corners of beaks and eyelids, and occasionally at the dorsal surface of the feet; and rough feathers (*Figure 3*).[22,29] Pantothenate-deficient chicks also exhibit ataxia (falling down to one side) or remain in a squatting position[30] with demyelination of the motor neurons with absent neural lesions;[29,31] degeneration of cell lining of the duodenal crypts of Lieberkuhn;[31] and compromised immune functions with microscopic changes in lymphoid tissue. The change is accompanied by lymphoid cell necrosis in the bursa of Fabricus and thymus, and a lympholytic paucity in the spleen.[31]

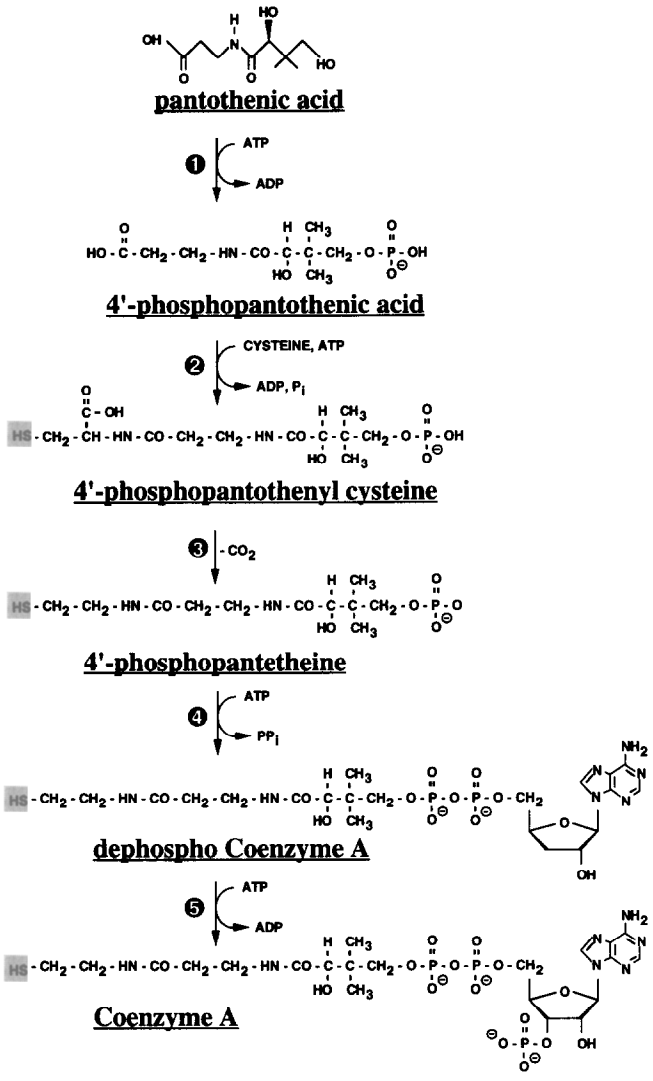

Figure 2 The biosynthetic pathway for CoA from pantothenate.

Similarly, pantothenate-deficient turkey poults[30] have shown dermatitis around the beak, whereas quails do not exhibit any outward signs other than decreased weight gain and poor feathering.[32] Ducks exhibit only decreased weight gain and an exudate from the eyes.[33]

Pigs exhibit loss of hair, reddening of skin, change of hair color, excessive nasal secretion, changes in tongue, anorexia, stunted growth, locomotor abnormalities, and excessive colitis.[34–42] The locomotor abnormality observed in pigs in the early stage of pantothenate deficiency is referred to as "goose-stepping" (*Figure 4*).[34,35] The pigs affected raise hind legs rapidly after put down, and placing weight on them appears painful. This is associated with chromatolysis of the dorsal root ganglion cells and demyelination.[34,35] Diarrhea associated with extensive colitis in pantothenate-deficient pigs is characterized by hyperemia, edema, bleeding, and increased size of lymphoid follicles, formation of small ulcers, and inflammatory changes in the large intestine.[34,39] The effects of pantothenate deficiency on food intake, intake of other vitamins, enteromicrobial growth, or on the immune response in relation to colitis need further examination.

Rats and mice have most frequently been studied for pantothenate metabolism. Rats deficient in pantothenate exhibit skin ulcers; greying, change of color, and roughening of hair coat, and hair loss; bloody whiskers with porphyrin, nervous disorders; duodenal inflammation and adrenal necrosis.[43–51] Guinea pigs showed a roughening of the hair coat, but no depigmentation.[52] Paralysis of the hind legs seen in pantothenate-deficient mice was associated with myelin degeneration of the sciatic nerves and the spinal cord.[50] Adrenal necrosis and altered adrenal endocrine functions observed in pantothenate deficient rats[43,47] have not been reported at the similar magnitude in other animals such as chicks,[31] pigs,[35,38] and dogs.[53–55] Adrenal cortices of pantothenate-deficient rats become large, with regression of cells in the zona reticularis and fasciculata, whereas ketosteroids are drained (*Figure 5*),[43] and eventually production of glucocorticoid is impaired under stress.[47] Animals such as mice, which are more sensitive to pantothenate deficiency than rats,[50] have been suspected to die before adrenal lesions develop. Hemorrhagic adrenals have also been reported in guinea pigs,[52] which are sensitive to pantothenate deficiency to the extent that adult females fed a pantothenate-deficient diet die between 10 and 41 days and, pregnant females die between 9 and 16 days.[56]

Pantothenate-deficient rats have liver cells shrunken and dying[43] and do not accumulate fat as fish,[57] dogs,[54] and cats.[58] Pantothenate deficient rats[43] have kidneys with "clumped" mitochondria, whereas dogs,[54] and pigs[38] show congested medulla that later hemorrhage.

Pantothenate-deficient animals including dogs, calves, and rats demonstrate a high incidence of spontaneous infections, morbidity, and a decreased antibody titer after introduction of an antigen. The decreased serum antibody titer in response to the injection of sheep erythrocytes was related to a decreased percentage of antibody-forming cells in the spleen and a mottled thymus,[54] and was corrected when pantothenate was supplemented.[55] Calves[59] and monkeys[60] deficient in pantothenate also show signs similar to those reported in other animals:[53,61] roughening of the hair coat, scaly dermatitis around the eyes,[59] greying and roughening of the hair coat, hair loss, diarrhea, and muscular weakness of the hind legs.[60] The weakness of the legs is related to a degeneration of the myelin around the sciatic nerve, and in the spinal cord.[59]

Fish exhibit dermatitis in the form of eroded skin, and a gill disease manifested by clubbed, exudate-covered gill lamellae.[57,62–64] Pantothenate-deficient fish[57] exhibit fat accumulation or fatty degeneration in the liver, as do cats[58] and dogs;[54] and "clumped" mitochondria in the kidney, as seen in rats.[43]

Pantothenate requirements of various species

Nutritional requirements are different from nutritional allowances, recommendations or guidelines, as the latters usually include safety margins beyond the minimal requirement.[127–131] Two prerequisites to determining the nutritional requirement, i.e., understanding bioavailability, and

Table 1 Representative signs of pantothenate deficiency in selected species

Species	Visible signs[1]	Histopathological abnormalities	References
Humans	Depression; personality changes; frequent infection; fatigue; sleep disturbances	Cardiac instability; abdominal pains; neurological disorders ("burning feet"); Reye-like syndrome; muscle weakness	23,24,25,26,27,28
Chicks	Dermatitis at corners of beak and eyelids; rough feathers; retarded growth; ataxia	Thymus involution; distended gall bladder; demyelination of motor neurons; moderate duodenal ulcerations	22,29,30,31
Swine	Loss of hair; reddening of skin; excess nasal secretion; changes in tongue; diarrhea; GI bleeding; locomotor abnormalities in gait ("goose-stepping")	Extensive colitis and small ulcers; inflammatory changes in large intestine; chromatolysis of dorsal root ganglion cells; demyelination of peripheral nerves	28,29,34,35,36,37,38, 39,42
Rats/mice	Skin lesions; greying of hair and bald patches; red "porphyrin" whiskers; paralysis of hind legs	Adrenal lesions; lipid depleted, shrunk and dying cells	43,44,45,46,47,48,49,50
Fish	Clubbed gills; intralamellar proliferative lesions; listless	Fused gill lamellae covered with exudate; fatty liver; kidneys deposited with glycogen and hyaline bodies; clumped mitochondria	57,62,63,64

[1]All species exhibited anorexia and a decreased growth rate.

sensitive and specific parameters that indicate nutritional status are lacking for pantothenate. Many factors such as strains of animals, forms of pantothenate supplemented, supplementation methods such as dietary versus injection, and use of antibiotics contribute to the variation of the requirement.

Although many studies in which pantothenate requirements were determined did not clearly distinguish the pantothenate requirement from the allowances, this review attempts to focus on the requirement when possible. Also, studies in which pantothenate was injected into animals are not included in this review because of uncertainty in metabolic conversion of different sources and forms of dietary pantothenate. Reports in which antibiotics were administered are also excluded from the summary.

Pantothenate requirements of young animals are often determined based on weight gain than the relief of deficiency signs, because of sensitivity. Weanling rats showed no deficiency signs when fed a diet containing 2 mg pantothenate/kg diet, but their weight gain did not plateau until more than 8 mg pantothenate/kg diet was fed.[65] Similarly, a lower dietary pantothenate intake is required to prevent dermatitis and other deficiency signs in chicks than to achieve maximum growth.[29,65–73] Of the visible deficiency signs, only normal feathering (particularly in pheasants and quails) requires as much or more pantothenate than maximum growth.[69,70]

Pantothenate requirements of growing young animals, range 8–15 mg/kg feed for different species and strains (*Table 2*). In early studies, many investigators used more than one strain in each experiment, and then chose the most susceptible strain in subsequent experiments. For example, mice of the C_{57} strain had a maximum growth rate when a diet contained at least 6 mg pantothenate/kg feed, but C_3H mice required 30 mg/kg to reach the maximum growth.[48,49] Different strains of chickens also show measurable differences in the pantothenate requirement for maximum growth.[66] Regardless of the species, however, the rapidly growing strain has the higher requirement than the slowly-growing strain.[49]

Figure 3 Chicks deficient in pantothenate show dermatitis around beak and rough feathers. (Courtesy of Dr. Duane Ullrey.)

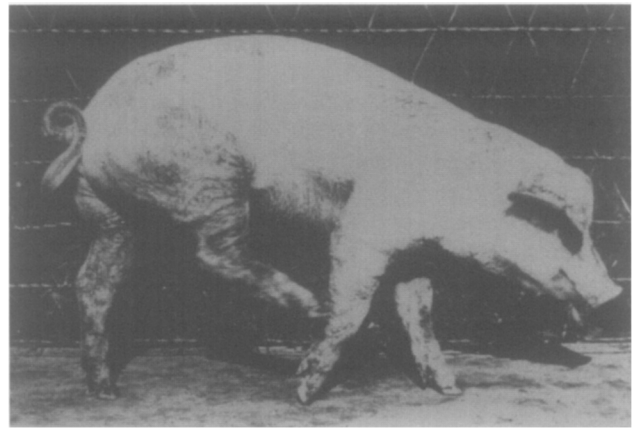

Figure 4 "Goose-stepping" as a sign of pantothenate deficiency in pigs. (Courtesy of Dr. Duane Ullrey.)

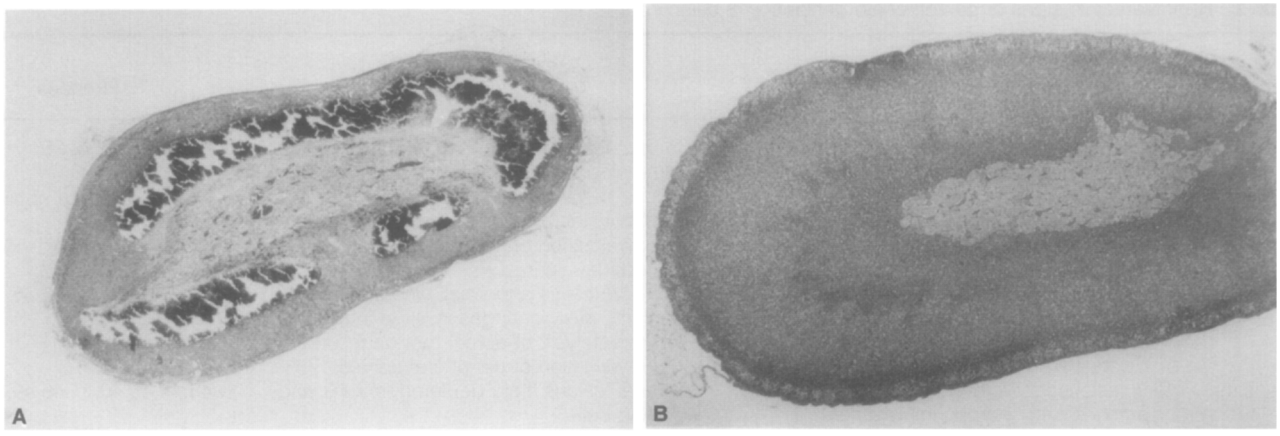

Figure 5 Adrenal necrosis observed in pantothenate-deficient rats (A) compared with healthy rats (B).[133]

Pantothenate requirements of the ruminant seem to be met by rumenal microorganisms that are capable of producing pantothenate.[74,75] Veal calves fed milk alone did not differ from those fed milk supplemented with 17 mg pantothenate/kg weight.[74] Balance studies showed that the amount of pantothenate excreted in the milk of lactating cows was about twice their dietary intake of the vitamin.[75] Furthermore, pantothenate concentration in the rumen of cows, and the rumen and reticulum of sheep[76] is about 20 to 30 times more concentrated than that in the diet. It is not certain, however, whether dietary pantothenate for feed-lot calves is really adequate,[77] especially to keep mortality low under stress during transportation.

Contribution of pantothenate synthesized by intestinal microflora to the host has frequently been overestimated in assessing pantothenate nutriture in mammals. Balance studies with humans,[78–80] and rats[81,82] do not support the significance of the availability of the pantothenate synthesized by intestinal microflora because pantothenate excreted in urine at no time exceeds dietary intake. When fed suboptimal amounts of dietary pantothenate, conventional chicks showed more severe signs of deficiency than germ-free chicks.[83,84] To achieve the same body weight and prevent deficiency signs, the germ-free chicks required only two-thirds the amount of pantothenate needed by the conventional chicks. These data suggest that either pantothenate synthesized by the intestinal microflora was not available to the host or a part of dietary pantothenate was destroyed by the microflora.

Studies that measured both weight gain and food intake in young and growing animals suggested that decreased food intake was not solely responsible for the lower weight gains in pantothenate deficiency.[68] Chicks pair-fed a diet containing adequate amounts of pantothenate with those fed pantothenate deficiency diets developed no deficient signs (e.g., dermatitis, exudate on eyelids).[29]

Pantothenate requirements for breeding have been studied in swine, chickens, turkeys, and rats. In general, the effect of pantothenate deficiency is more serious in offspring than in dams. Adult gilts fed a diet marginal in pantothenate (5.9 mg/kg diet) showed almost no signs of pantothenate deficiency, but had a greater than 50% decrease in the number of pigs weaned per litter farrowed, weaning weight of the litters, and total pantothenate concentration in their milk.[40] Furthermore, a diet marginally adequate for the first generation gilts produced significant differences in the reproductive performance by the third generation.[41] Chickens and turkeys had a greater difference between maintenance levels for the adults, and breeding requirements for viable offsprings than other species. Chicks fed a low pantothenate diet resulted in decreased hatchability with successive hatchings.[22,73] Rats fed a pantothenate deficient diet during 3 weeks of pregnancy produced pups with lower body and organ weights, with higher resorption rate than the control, even though the dams body and organ weights did not differ from the control.[132] The results are suggested as due to impaired placental endocrine functions and inadequate supply of pantothenate for fetal growth, because pantothenate deficient dams had a lower plasma progesterone, elevated plasma cholesterol, elevated placental cholesterol, and lower placental acetylcholine concentrations compared with the control.[132]

The adult nurse bees appear to have no requirement for dietary pantothenate,[85] although they must have a high demand for feeding the larvae. Unlike other species, a pantothenate free synthetic sugar diet had no adverse outcome on brood rearings, even after five broods were followed. Because the amount of pantothenate in royal jelly exceeds the bees' dietary intake from pollen, bees are speculated to have a source for pantothenate other than the diet.

Factors affecting pantothenate requirements

Age of experimental animals

A large decrease in the requirement for pantothenate is seen with increasing age, reflecting a lower requirement for maintenance than for growth.[86–90] Deficiency signs such as a decreased weight gain and greying of hair, appeared at a younger age, and at higher pantothenate intakes in the young rats than in old rats. Furthermore pantothenate deficiency signs frequently disappeared as rats and mice aged, which is consistent with a decreased requirement with age.[49,89] Adult rats fed a pantothenate deficient diet for 4 weeks gained less weight than the controls, and exhibited roughening of the fur.[91] In this study, free pantothenate concentration was decreased about 90% in most tissues,

Table 2 Pantothenate requirements of various species

Species/strains	Minimum requirement (mg/kg diet)	Determinants	References
Humans			
Adults	4–7[1]	Usual intake; urinary excretion	127
Infants	2–3[1]	Human milk composition	
Chickens			
chicks-young	7.8–10.0	Weight gain; feed efficiency; gain in fat; production energy; decrease in heat increment	29,65,68
laying hens	1.9–8.8	Egg production; maintenance of weight; no deficiency signs	67
breeding chickens	8.9–12.1	Hatchability; viability of offspring	22,67
Quail			
Bob-white	11.5–12.6	Weight gain; feathering	32,69,70,71
Japanese, young	10.0–30.0	7.5 for growth; 10–30 for normal feathering	
Japanese, adult/breeders	15.0	Fertility; hatchability	70
Geese			
young	12.6	Weight gain; mortality	72
Ducks			
14–18 days old	11.8	Weight gain	33
Turkey			
poults, 7–23 days old	10.5	Weight gain; no dermatitis of the mouth	30
hens, 1–3 years old	16.0	Fertile eggs; hatchability	90
Pheasants			
young chicks	11.5	Weight gain; mortality; featherings	69
Swine			
baby, 10 kg	12.5	Weight gain; no diarrhea and locomotor abnormalities	90,130
young	8.1–13.4	Weight gain; food conversion; no deficiency signs	39,65,94,104
breeding sows	11.9–12.5	Litter birth weight; litter weanling weights	40,41,90
Rats			
weanling	8.0–10.0	Weight gain; acetylation of sulfanilamide	86,87,128,129
Mice			
weanling	6.0–30.0 (strain dependent)	Weight gain; no deficiency signs	49
Guinea pig			
young	15.0–20.0	Weight gain	52
Cats			
young, 3 mo	5 mg	Weight gain; acetylation of sulfanilamide	58
Catfish			
Channel, fingerlings	10.0–15.0	Weight gain; food conversion; clubbed gills	62,63,131
Bees[1]			
nurse bees, which provide	0.0	High number of sealed and unsealed food for larvae through first four broods	85

[1]mg/day.

whereas the total CoA content was not significantly lower in liver, muscle, or other tissues in the pantothenate-deficient rats than in the control. The observation is consistent with the hypothesis that the decreased weight was principally due to pantothenate deficiency per se rather than through the altered total CoA content of tissues.[91]

Differences in pantothenate requirement by age have also been reported between young chicks and laying hens,[22] between turkey hens and turkey poults,[30,73] and between young puppies and adult dogs.[53] Puppies fed a pantothenate-deficient diet developed erratic feeding behavior with a decreased weight gain after 2 to 3 weeks of the experiment, whereas young adult dogs showed decreased appetite after 7 to 8 weeks and collapsed after 13 weeks of the study.[53] Pantothenate requirement of guinea pigs is the highest during the first few days after birth.[52] Guinea pigs are so sensitive to the pantothenate deficiency that even adult guinea pigs fed a pantothenate-free diet lose weight rapidly. The mean survival time of only 24 days of pantothenate deficient guinea pigs corresponds to the fall of liver CoA to about 50% of the control.[56]

Low pantothenate requirements appear to be related to slow-growing species or measurement done at a stage of growth plateau. The pantothenate requirement for the Shetland pony (3.2 mg pantothenate/kg feed) was derived from studies with ponies of 6 months to 1 year of age.[92] Adult humans consumed a synthetic pantothenate-free diet supplemented with a metabolic antagonist (omega-methyl pantothenate) for 4 and 12 weeks before developing even mild symptoms of pantothenate deficiency: personality changes, fatigue, parethesias, and impaired motor coordination.[24,25] In the absence of a more sensitive biochemical parameter of pantothenate deficiency, it has not been possible to determine the human pantothenate requirements.

Analytical methods

Many early studies used natural feedstuffs (e.g., corn, soybean meal, or fish meal) to formulate a pantothenate-low basal diet and then supplemented with known amount of the vitamin.[92–94] The pantothenate content was generally determined by a pantothenate-requiring bacteria[95] after degrading CoA and other pathway intermediates to pantothenate with a crude preparation of "chicken liver enzyme."[96]

The microbiological assays for pantothenate are, however, known to have large variabilities related to the choice of both microorganism, and degradative procedures.[65,84] The development of a radioimmunoassay[97] enzyme immunosorbent assay,[98] and preparation of pantetheinase[99] by Wyse and her collaborators, have eliminated significant sources of the reported variabilities.[100]

Use of antibiotics

Antibiotics such as penicillin, chlortetracycline, and streptomycin affect pantothenate requirements. Treatment of pantothenate deficient animals of several strains with antibiotics increased weight gain. The observation is consistent with other evidences in which intestinal microflora do not contribute pantothenate requirements of the host. Weanling rats[101–103] fed a pantothenate-deficient diet alone had 45% of the optimal weight gain, but those treated with chlortetracycline and penicillin had weight gains of 55% and 60% of the optimal rates, respectively.[101] The pantothenate-sparing effect of the antibiotics was not, however, seen in rats given optimal amounts of pantothenate.[102–103] Similar effects of antibiotics have been reported in weanling pigs[104] and turkey poults[105] fed a pantothenate-deficient diet. Other studies that reported little or no effect of antibiotics on the pantothenate requirement,[94,106,107] used dietary pantothenate levels above the requirement.

The effect of antibiotics on pantothenate nutriture is due solely to their actions on enteromicrobes, because the pantothenate sparing effect of antibiotics was more prominent when pantothenate was given orally.[102,103,108] Oral antibiotics increased the amount of pantothenate in the rat intestine,[102] and in the liver and urinary and fecal excretions.[109] A reduced pantothenate requirement as determined by growth and lack of deficiency signs observed in the germ-free chick compared with the conventional chick confirms that the effect is related to bacterial growth,[88] and possibly a decreased catabolism of pantothenate. Alternatively, the enhanced growth by the use of antibiotics was hypothesized as due to prevention of duodenal ulcers that were seen in pantothenate deficiency and caused by microorganisms,[51] or prevention of microbial destruction of the vitamin.

Dietary pantothenate intake versus tissue CoA content

A sensitive and specific nutritional indicator would be a decrease in the content of coenzyme (either total CoA, unacylated CoASH, a specific acyl CoA derivative, or bound phospho-pantetheine) in a sensitive tissue. Although the relationship between the dietary intake and tissue pantothenate and CoA content has been examined in a number of species, the decrease of total CoA content in the tissues examined does not correlate well with the development of deficiency signs. For example, in Roth-Maier's studies on chickens and pigs,[110] levels of free and "bound pantothenate" (a term that referred to the amount pantothenate present as CoA and other pantothenate derivatives) in the liver were the same for animals consuming either pantothenate-deficient or excess pantothenate diet.[65] In adult rats fed a pantothenate-deficient diet for 4 weeks, the total CoA content of the liver and other tissues was resistant to pantothenate deficiency, although the pantothenate contents of the tissues decreased by more than 90%.[91] In studies in which liver total CoA did fall, the decline reached a plateau and ceased.[111] However, a good correlation between decreased liver pantothenate and the development of dermatitis in chicks was observed.[66]

In contrast, the decline of total CoA content of tissues in younger animals, particularly that of skeletal muscle, appears to correlate closely with decreased dietary pantothenate intake. The total CoA content of skeletal muscle of mice,[112] rats,[113] puppies,[53] and hens[114] declined more than liver CoA contents. The rapid fall of muscle CoA, and the relatively large muscle mass, has led to the suggestion that muscle may act as a pantothenate reservoir. In view of these studies, the use of the rate of in vivo acetylation of sulfanilamide or para-aminobenozate (dependent on the acetyl CoA content of the liver), as a functional assay of pantothenate deficiency should be further evaluated.

The ability of the liver, and possibly other tissues, to maintain nearly constant total CoA contents despite deficient dietary intake of pantothenate could be a reflection of the feedback mechanism for the regulation of CoA biosynthesis. A large number of investigators have demonstrated feedback inhibition of pantothenate kinase by CoASH, acetyl CoA, other acyl-CoA and/or CoA precursors.[1,115–122]

Variations in the reported sensitivity of pantothenate kinase to inhibitors may reflect the differences among tissues, species, or methods used by various laboratories. By this mechanism, the decline of pantothenate to serve as a substrate for pantothenate kinase would be counterbalanced by deinhibition of pantothenate kinase as CoA levels started to decrease.

Because pantothenate deficiency is also accompanied by decreased food intake, hormones that regulate tissue metabolism in response to fasting and feeding may also play a role in maintenance of constant CoA levels in tissues.[123–124] During fasting, pantothenate uptake by liver is stimulated by the rise in glucagon and pantothenate conversion to CoA is stimulated by glucagon and cortisol.[125] Synthesis of CoA is also increased in the heart during fasting, although pantothenate uptake is decreased.[126] Degradation of CoA in the liver may also be regulated in response to fasting or changes in metabolic state,[120,123,124] and there is an enhanced retention of pantothenate by the kidney during fasting.[126]

Conclusion

Comparisons of the pantothenate requirement among species involve comparing studies that used different criteria for the state of deficiency, animals of different ages, and different means of determining dietary pantothenate intake. In spite of the wide variation in experimental conditions, a

high degree of similarity was seen in the pantothenate requirement of different species.

1. In studies with young and growing animals in which weight gain was the principal basis for establishing the dietary requirement for pantothenate, the requirement was generally between 8 and 15 mg/kg diet. The decreased rate of weight gain resulting from pantothenate deficiency was partly due to anorexia and decreased food consumption.
2. All species studied exhibited deficiency signs affecting hair color, hair loss, feather development, skin, or gills. Development of normal feathering in birds (quail, pheasants, turkeys, chicks, etc.) required a higher dietary intake of pantothenate than normal weight gain.
3. Locomotor abnormalities, especially those in the hind legs, are exhibited by most pantothenate deficient species, and appear to be associated with demyelination. In swine, but not in other species, the abnormalities are also associated with chromatolysis of the dorsal root ganglion cells.
4. Most species studied developed problems with the intestinal tract. However the exact site varies between species.
5. A few species, for example, mouse have shown as large differences in pantothenate requirement between strains as exists between species.
6. Pantothenate requirements decrease with age or after the growth plateau is attained. However, adult pantothenate requirements are not really known for most species because of the lack of an acceptable specific parameter for pantothenate deficiency other than weight gain.
7. Pantothenate requirement for breeding, as determined by viability of offspring through successive generations are generally higher than those for the young and growing of the species.
8. Ruminant species obtain pantothenate partly from microbial synthesis in the rumen. However, there is also pantothenate destruction in the rumen, and the amount of dietary intake reaching the duodenum may not be sufficient in animals on a pantothenate-free diet.
9. CoA is conserved mainly in liver, and to a lesser extent in other tissues. Mechanisms that contribute to the conservation of CoA in liver (and heart) include (1) feedback regulation through inhibition of pantothenate kinase by CoASH, acetyl-CoA, or a related metabolite, and (2) hormonal regulations of CoA levels in liver by glucagon, insulin and glucocorticoids, and in heart by insulin. Differences among species in the regulation of CoA biosynthesis and degradation have not been explored.

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