15
Pantothenic Acid and Coenzyme A

Key discussion topics

- The biological activity of pantothenic acid is attributable to its incorporation into the molecular structures of coenzyme A and acyl carrier protein.
- A multivitamin transporter mediates the uptake of pantothenate, biotin and lipoate by apparently all cell types.
- Many diverse cellular proteins are modified by the covalent attachment of lipids donated by CoA or requiring CoA for their synthesis.

15.1 Historical overview

In 1933 R. J. Williams and his research team isolated from a variety of biological materials an acidic substance that acted as a growth factor for yeast. Williams' team elucidated the chemical structure of the purified substance and named it pantothenic acid because of its apparently widespread occurrence (Greek *pantos*, everywhere). Pantothenic acid was established as a vitamin in 1939, when it was shown to be identical to a 'filtrate factor' required by rats for normal growth, and to a chick anti-dermatitis factor. The chemical synthesis of pantothenic acid was reported by Williams and Major in 1940 and its biochemical role as a constituent of coenzyme A was identified by Fritz Lipmann in 1947.

15.2 Chemistry

Structures of pantothenic acid and compounds containing a pantothenate moiety are shown in Fig. 15.1. Pantothenic acid comprises a derivative of butyric acid (pantoic acid) joined by a peptide linkage to the amino acid β-alanine. In nature, pantothenic acid occurs only rarely in the free state, but it is very widely distributed as an integral part of the structures of coenzyme A (CoA) and 4-phosphopantetheine. The latter serves as a covalently attached prosthetic group of acyl carrier protein. The steric configuration of the pantothenic acid moiety is important for enzymatic recognition in biochemical reactions involving CoA and acyl carrier protein.

15.3 Dietary sources and bioavailability

15.3.1 Dietary sources

Coenzyme A is the major pantothenic acid-containing compound present in foods of both animal and plant origin, accompanied by small amounts of other bound forms (phosphopantothenic acid, pantetheine and phosphopantetheine). Notable exceptions are human and bovine milk in which free (unbound) pantothenic acid constitutes around 90% of the total pantothenate content.

Pantothenic acid is widely distributed in foods. It is particularly abundant in animal organs (liver, kidney, heart, brain) and also in egg yolk, peanuts

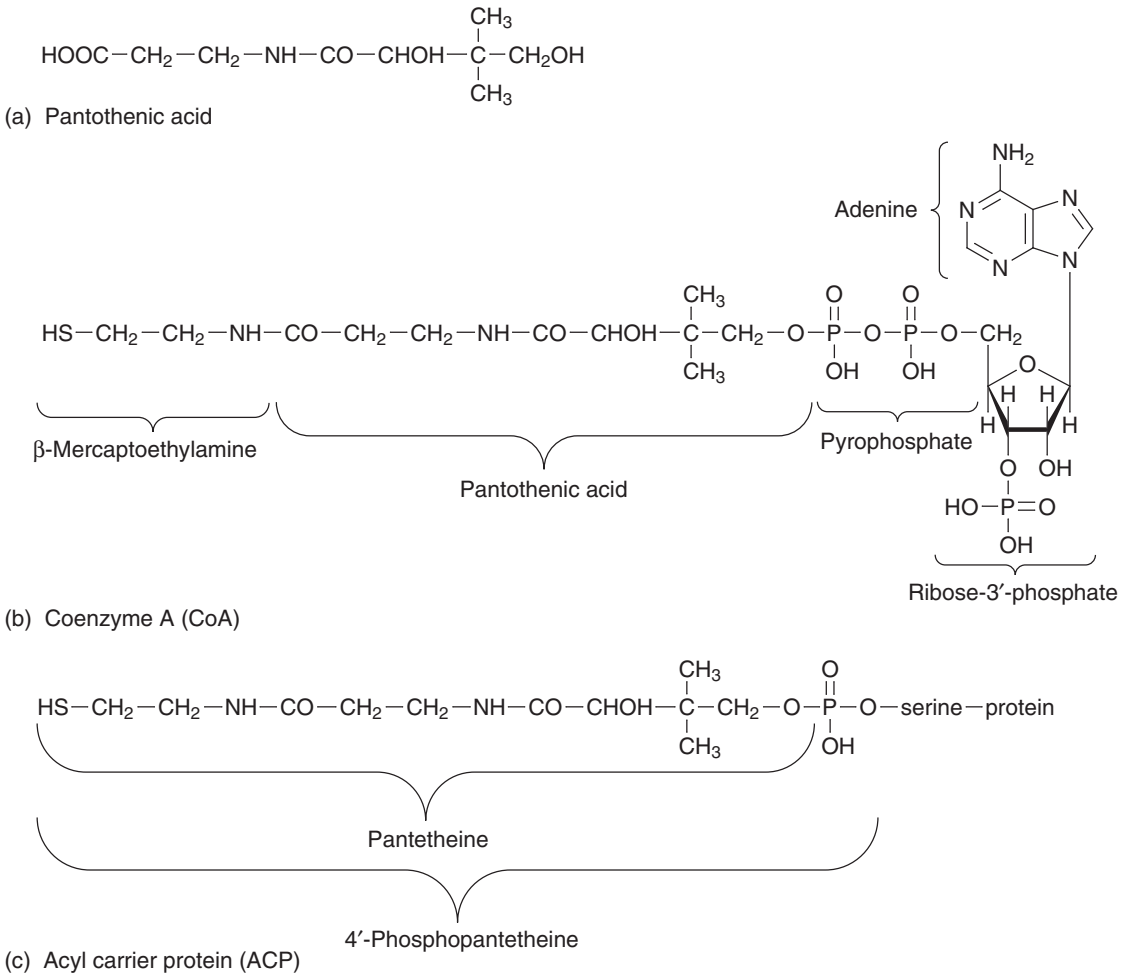

Fig. 15.1 Structures of (a) pantothenic acid, (b) coenzyme A and (c) acyl carrier protein.

and broad beans. Lean meat, milk, potatoes and green leafy vegetables contain lesser amounts, but these will be important food sources if consumed in sufficient quantity. Highly refined foods such as sugar, fats and oils, and cornstarch are totally devoid of the vitamin.

15.3.2 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% (Tarr *et al.*, 1981).

15.4 Absorption, transport and metabolism

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.

15.4.1 Digestion and absorption of dietary pantothenic acid

Ingested CoA, the major dietary form of pantothenic acid, is hydrolysed in the intestinal lumen to pantetheine by the non-specific action of pyrophosphatases and phosphatase. Pantetheine is then split into pantothenic acid and β-mercaptoethylamine by the action of pantetheinase secreted from the intestinal mucosa into the lumen (Shibata *et al.*, 1983). Absorption of the liberated pantothenic acid takes place mainly in the jejunum, although there is no significant difference in the rate of uptake in the upper, middle or lower intestine. Within the alkaline medium of the intestinal chyme, the vitamin exists primarily as the pantothenate anion.

Fenstermacher & Rose (1986) evaluated the properties of pantothenic acid absorption in the intestine of rat and chicken using several experimental approaches. Sodium dependency and saturation kinetics were demonstrated for the unidirectional influx of [^{3}H]pantothenic acid across the brush-border membrane of rat jejunum. Potassium gradients were employed in isolated ATP-depleted chicken enterocytes to evaluate the effects of cell membrane potential on pantothenic acid uptake. Uptake was not influenced by the artificially induced electrical gradients and so it appeared that the coupling ratio of Na^+:pantothenate$^-$ is 1 : 1, making the process electroneutral. The process by which pantothenic acid exits the enterocyte at the basolateral membrane has not been established.

The sodium-dependent multivitamin transporter

A so-called sodium-dependent multivitamin transporter (SMVT) which mediates placental and intestinal uptake of pantothenate, biotin, certain biotin analogues and the essential metabolite lipoate has been cloned from rat (Prasad *et al.*, 1998) and human (Wang *et al.*, 1999) placenta and from rabbit intestine (Prasad *et al.*, 1999). Transfection of the cloned intestinal cDNA into COS-7 cells has confirmed that the functional characteristics of the cloned transporter are similar to those observed in native intestinal membranes regarding substrate specificity, kinetics and inhibitor profiles (Chatterjee *et al.*, 1999). 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. mRNA transcripts of SMVT were shown to be present in all of 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 (Prasad *et al.*, 1998). Chatterjee *et al.* (1999) identified four distinct variants (I–IV) of the SMVT and determined their tissue distribution. Variants II, III and IV were present in the small intestine, with II predominating; variant I was present in the placenta, but not in the small intestine.

The number of Na^+ ions interacting with SMVT was calculated to be 1.6 for the uptake of pantothenate and 2.0 for the uptake of biotin (Prasad *et al.*, 1999). This indicates that, for every pantothenate or biotin molecule transported, two Na^+ ions are co-transported, i.e. a Na^+:vitamin stoichiometry of 2:1. Since both pantothenic acid and biotin are monovalent anions at physiological pH, the transport process involving this carrier is electrogenic. Thus, both the Na^+ gradient and the potential difference across the brush-border membrane drive the transport process.

Whether the SMVT is actually responsible for pantothenate uptake by the enterocyte *in vivo* is not

known for certain. If it does fulfil this function, the reason that previous studies failed to show the electrogenicity of the transport process may be that the experimental concentrations of Na^+ were not low enough to observe the sigmoidicity of the plot of the Na^+ concentration/uptake rate (Prasad *et al.*, 1999).

Absence of adaptive regulation of pantothenic acid absorption

Unlike the other water-soluble vitamins which are absorbed by specific carrier-mediated systems (ascorbic acid, biotin and thiamin), the absorption of pantothenic acid is not adaptively regulated by its level of dietary intake (Stein & Diamond, 1989). The absence of clear-cut deficiency symptoms in humans and the lack of toxicity at high doses could explain why an adaptively regulated absorption mechanism has not evolved for pantothenic acid.

15.4.2 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 (Sorrell *et al.*, 1971). Said *et al.* (1998) showed that human colonic epithelial NCM460 cells took up pantothenic acid by a Na^+-dependent, carrier-mediated process that was shared by biotin. The existence of this uptake system was corroborated by the identification of mRNA transcripts complementary to the cloned intestinal cDNA in rat colon (Chatterjee *et al.*, 1999).

15.4.3 Post-absorptive metabolism

After absorption, free pantothenic acid is conveyed in the portal circulation to the liver where the majority is taken up by sodium-coupled, secondary active transport (Smith & Milner, 1985). The heart takes up pantothenic acid by a similar mechanism (Lopaschuk *et al.*, 1987). Beinlich *et al.* (1990) observed that pantothenic acid inhibited biotin accumulation in the perfused rat heart, suggesting that these two vitamins share a common uptake mechanism in the heart. Uptake of pantothenic acid by red blood cells, unlike other tissues and cell types, takes place by simple diffusion (Annous & Song, 1995).

In mammalian tissues (but not in red blood cells) CoA is synthesized from pantothenic acid in five enzymatic steps. Three substrates are needed to synthesize CoA: pantothenic acid, ATP and cysteine. The rate-controlling step in the synthesis is the conversion of pantothenic acid to 4′-phosphopantothenic acid by pantothenate kinase. Tissue levels of CoA are kept in check by feedback inhibition of pantothenate kinase by CoA, acetyl-CoA or a related metabolite (Robishaw & Neely, 1985).

In the event of a drastically reduced intake of pantothenic acid, such as would occur during food deprivation, the liver, and possibly other tissues, is able to maintain nearly constant CoA levels for some considerable time. In fasting rats, pantothenic acid uptake by the liver is stimulated by the natural rise in glucagon, and incorporation of pantothenic acid into CoA is stimulated by glucagon and cortisol (Smith & Savage, 1980). In contrast to the liver, uptake of pantothenic acid by heart and skeletal muscle of fasting rats is reduced, and yet the rate of pantothenic acid conversion to CoA is increased (Reibel *et al.*, 1981). Evidently, myocardial and muscle CoA synthesis is not governed by the availability of pantothenic acid to these tissues, but rather is controlled intracellularly by regulation of enzymes involved in the CoA synthetic and/or degradative pathways. Reibel *et al.* (1981) postulated that the large amounts of pantothenic acid stored in muscle can be shifted to the liver where endogenous concentrations of the vitamin are normally low.

15.4.4 Brain homeostasis

Spector *et al.* (1986) measured the unidirectional influx of [^{3}H]pantothenic acid across cerebral capillaries (the anatomical locus of the blood–brain barrier) using an *in situ* rat brain perfusion technique. Transport took place by a low-capacity, saturable system that was inhibited by biotin and medium-chain fatty acids. The data suggested that most, if not all, of the pantothenic acid in brain gains entry through the blood–brain barrier. The half-saturation concentration for the transport process was 19 μM, which is an order of magnitude greater than the plasma concentration of 2 μM. Normally, the concentration of plasma pantothenic acid is regulated by the kidneys,

but if one were to increase plasma levels by parenteral means, unnaturally high concentrations would gain access to the extracelluar space of brain. Thus transport across the blood–brain barrier plays no role in the regulation of brain CoA levels; rather, subsequent enzymatic steps in the brain cells regulate the conversion of pantothenic acid to CoA. This conversion is very slow, unlike that in other tissues such as the liver and heart, and could at least partly explain why the brain is the organ most difficult to deplete of pantothenic acid and CoA. The inhibition of pantothenic acid transport by biotin provided further evidence that these two vitamins share the SMVT characterized by Prasad *et al.* (1998). The inhibitory effect of medium-chain fatty acids has clinical significance, as in several disease states (e.g. liver failure) there are enormous increases in plasma concentrations of medium-chain and long-chain fatty acids.

The entry of pantothenic acid from blood into cerebrospinal fluid via the choroid plexus and from the extracellular space of brain into brain cells themselves are both saturable transport processes (Spector, 1986).

15.4.5 Placental transport

Evidence of an electrogenic Na^+-pantothenate (2:1) co-transport mechanism was reported in human placental microvillous membrane vesicles (Grassl, 1992) and two human placental cell lines (Prasad *et al.*, 1997). The system was inhibited by biotin and lipoate. Prasad *et al.* (1999) deduced from amino acid sequencing that the SMVT involved in Na^+-coupled transport of pantothenate and biotin in the intestine is also shared by these vitamins in placental transport.

15.4.6 Renal reabsorption and excretion

Reabsorption of pantothenic acid in the brush-border membrane of the proximal convoluted tubule takes place by a carrier-mediated, Na^+-dependent transport system that is electrogenic and has a 2:1 Na^+:pantothenate$^-$ stoichiometry (Barbarat & Podevin, 1986).

Pantothenic acid derived from the degradation of CoA is excreted intact in urine. The amount excreted varies proportionally with dietary intake over a wide range of intake values (Tahiliani & Beinlich, 1991). Both fasting and diabetes result in decreased excretion (Reibel *et al.*, 1981), thus conserving whole-body pantothenic acid under these conditions.

15.5 Biochemical functions of coenzyme A and acyl carrier protein in cellular metabolism

15.5.1 Coenzyme A

Background information can be found in Section 4.1.

CoA (HS–CoA in biochemical reactions) forms energy-rich thioesters with weakly reactive carboxylic acids, so that the acyl (R–CO–) groups can participate in numerous biochemical reactions. Some of these reactions are involved in the release of energy from carbohydrates, fats and amino acids.

- In carbohydrate metabolism, the pyruvate produced by glycolysis must undergo an oxidative decarboxylation reaction with CoA to form acetyl-CoA (CH_3–CO–S–CoA in biochemical reactions) before the acetyl moiety can react with oxaloacetate to produce citrate in the tricarboxylic acid cycle.
- Another tricarboxylic acid cycle intermediate, α-ketoglutarate, undergoes an oxidative decarboxylation with CoA to form succinyl-CoA. Succinyl-CoA reacts with glycine to form (via an intermediate) δ-aminolevulinic acid, which is a precursor of the porphyrin ring system of haemoglobin and cytochromes.
- CoA is required at two steps in each cycle of the β-oxidation of fatty acids, in which two carbon units are removed per cycle to yield ultimately acetyl-CoA.
- In amino acid metabolism, leucine is deaminated to form the keto acid isovalerylformic acid, which reacts with CoA to yield a series of intermediates, ultimately giving rise to acetoacetic acid and acetyl-CoA.
- Acetyl-CoA is required for the acetylation of choline to form the neurotransmitter acetylcholine.
- The amino sugars D-glucosamine and D-galactosamine react with acetyl-CoA to form acetylated products, which are structural components of various mucopolysaccharides. For example, hyaluronic acid, which is found in connective tissue, the vitreous humour of the eye, and Wharton's jelly in the

umbilical cord, consists of alternating residues of *N*-acetyl-D-glucosamine and D-glucuronic acid.
- Chondroitin sulphate, found in the matrix of cartilage and bone, heart valves, tendons, and the cornea, is built up from sulphated esters of *N*-acetyl-D-galactosamine and D-glucuronic acid.
- The biosynthesis of cholesterol begins with the condensation of two molecules of acetyl-CoA to form acetoacetyl-CoA. The latter reacts with a third molecule of acetyl-CoA to form β-hydroxy-β-methylglutaryl-CoA (HMG-CoA), which in turn is reduced to mevalonic acid.

Mevalonic acid is an important intermediate because it gives rise to isoprenoids that are involved in the modification of functional proteins (Section 15.6). As well as being synthesized within the cell, cholesterol enters the cell from receptor-mediated uptake of plasma low-density lipoprotein (LDL). The cell must balance the endogenous and exogenous sources of cholesterol to avoid over-accumulation of the sterol, while sustaining adequate mevalonic acid synthesis. This balance is achieved through feedback regulation of at least two sequential enzymes in mevalonic acid synthesis, HMG-CoA synthase and HMG-CoA reductase, and also of LDL receptors (Fig. 15.2). In the absence of LDL, animal cells maintain high activities of the two enzymes, thereby synthesizing mevalonic acid for production of cholesterol as well as the essential isoprenoids. When LDL is present, the synthase and reductase activities decline by more than 90%, and the cells produce only the small amounts of mevalonic acid needed for the non-sterol end-products. When cellular sterol levels rise or when cell growth ceases and cholesterol demand declines, the LDL receptor gene is repressed, further averting cholesterol accumulation.

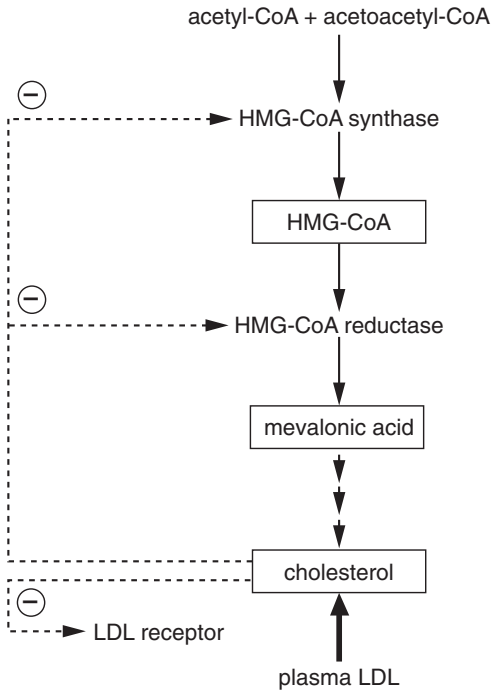

Fig. 15.2 Regulation of the mevalonic acid pathway showing cholesterol-mediated feedback repression of the genes for HMG-CoA synthase, HMG-CoA reductase and the LDL receptors.

15.5.2 Acyl carrier protein

Acyl carrier protein, as an integral part of fatty acid synthase, is involved in the biosynthesis of fatty acids. Apart from dietary fat, the major source of fatty acids in the animal body is carbohydrate, which is broken down to pyruvate by the glycolytic pathway in the cytoplasm of all cells. Pyruvate moves by passive diffusion from the cytosol into the matrix of the mitochondrion where it is (1) oxidized to acetyl-CoA and (2) carboxylated to oxaloacetate. Acetyl-CoA is the starting material for the synthesis of fatty acids. The formation of acetyl-CoA in the mitochondrion poses a problem because the enzyme complex required for fatty acid synthesis (fatty acid synthase) is located in the cytosol. The cell circumvents this problem in the following way. The acetyl-CoA and oxaloacetate react together to form CoA and citrate, and the latter is transported out of the mitochondrion to the cytosol. In the cytosol citrate reacts with CoA to form oxaloacetate and acetyl-Co. Acetyl-CoA, with the required amounts of ATP and NADPH, is now ready to serve as substrate to form palmitate.

The fatty acid synthase enzyme complex in vertebrates consists of two identical subunits, each with a molecular weight of 240 000 and each containing the full complement of enzymes required for fatty acid synthesis. Each subunit is totally inactive in synthesizing a fatty acid: only when the two subunits combine in an antiparallel orientation to form a homodimer is activity expressed. In addition to ACP, the fatty acid synthase complex contains condensing enzyme, which also possesses a free sulphydryl (–SH) group.

The involvement of ACP in fatty acid biosynthesis is depicted in Fig. 15.3. Malonyl-CoA is formed by the

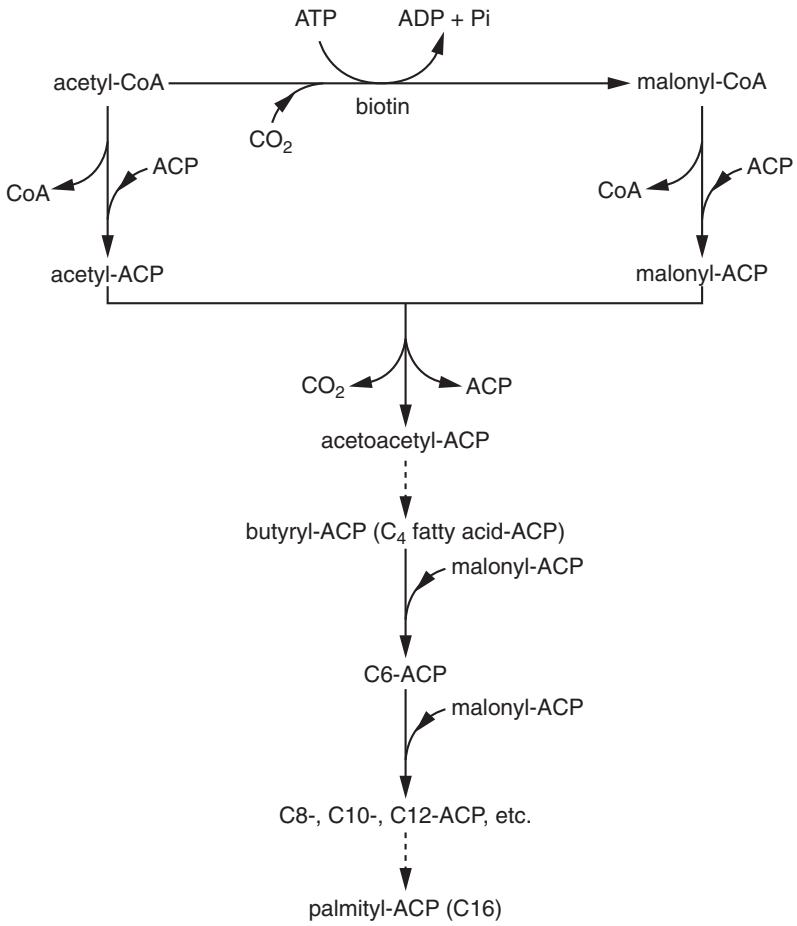

Fig. 15.3 The role of acyl carrier protein (ACP) in the biosynthesis of fatty acids. For simplicity, the contribution of condensing enzyme is not shown.

biotin-dependent carboxylation of acetyl-CoA and the acyl groups of acetyl-CoA and malonyl-CoA are transferred to the –SH group of acyl carrier protein (ACP). The resultant acetyl-ACP and malonyl-ACP molecules react together with the release of CO_2 to form acetoacetyl-ACP, which undergoes further reduction and dehydration reactions to yield butyryl-ACP. This, in turn, reacts with malonyl-ACP, with a repetition of the same sequence of events, to yield a six-carbon fatty acyl ACP derivative. The process is repeated, adding two carbon atoms at a time to the growing chain, until the palmityl derivative with 16 carbon atoms is formed. The ACP moiety then splits off and the palmitic acid is released. The palmitic acid can be lengthened by fatty acid elongation systems to stearic acid and even longer saturated fatty acids. Furthermore, by desaturation reactions, palmitate and stearate can be converted to their corresponding Δ^9 mono-unsaturated fatty acids – palmitoleic and oleic acids, respectively.

15.6 Physiological roles of coenzyme A in the modification of proteins

15.6.1 Protein modification

Many diverse cellular proteins are modified by the covalent attachment of lipids donated by CoA or requiring CoA for their synthesis. The modifications fall into three main categories: acetylation, acylation and isoprenylation (Magee, 1990; Casey, 1994). The alterations in protein structure may be relevant to the association of proteins with the plasma membrane or with subcellular membranes, protein–protein binding, or the targeting of proteins to specific intracellular locations. In some cases the modifications are co-translational, i.e. they take place on the growing polypeptide chain associated with the ribosome during protein synthesis; in other cases they are post-translational.

Most soluble proteins are acetylated at their amino termini as a means of altering their binding affinity

for receptors or other proteins. Internal acetylation of nuclear histones weakens their association with DNA. The two long-chain fatty acids most commonly attached to proteins are myristic acid (14:0) and palmitic acid (16:0). The enzyme linking myristate to amino-terminal glycine residues by an amide bond is *N*-myristoyl transferase, which has strict sequence requirements in the protein substrate. Palmitoyl transferases link palmitate to the side chains of cysteine residues by a thioester bond. The cysteine residues can reside at any point in the primary structure of the protein; there is little evidence for any specific sequence requirements. Unlike the highly stable amide linkages to myristate, modifications of proteins by palmitate occur in thioester or oxyester linkages that are subject to hydrolysis by esterases. Cycles of palmitoylation and depalmitoylation allow the modified protein to have a regulating function. Addition of an isoprenoid chain to the cysteine residue of the primary motif CAAX (C, cysteine; AA, an aliphatic amino acid; X, the carboxy terminal amino acid) is the first step in the modification of proteins bearing this C-terminal motif. Either the 15-carbon farnesyl or the 20-carbon geranylgeranyl chain is added, depending on the sequence of the CAAX motif.

Myristoylated proteins include G protein α subunits (signal transduction), ADP-ribosylation factors (vesicular transport), myristoylated alanine-rich C kinase substrate protein (cytoskeletal rearrangements), recoverin (vision), proteins of the immune system, and several enzymes. Palmitoylated proteins include G protein α subunits, many plasma membrane-anchored receptors, cytoskeletal proteins, gap junction proteins, neuronal proteins, and the enzymes acetylcholinesterase and glutamic acid decarboxylase. Palmitate modification is also a prerequisite for the budding of transport vesicles from Golgi cisternae. Isoprenylated proteins include Ras proteins (signal transduction), Rab proteins (vesicular transport), nuclear lamins A and B (assembly and stabilization of the nuclear envelope), G protein γ subunits, and the enzymes phosphorylase kinase and rhodopsin kinase.

15.6.2 Physiological implications of protein modification

The physiological implications of protein modifications involving coenzyme A are illustrated in the following examples.

Acetylation of β-endorphin

Amino-terminal acetylation plays an important role in regulating the biological activity of the brain neurotransmitter β-endorphin. This peptide has morphine-like analgesic activity and also affects sexual behaviour and learning. Acetylation deactivates β-endorphin by rendering it unable to bind to specific receptors. The modification is post-translational and occurs before or during the packaging of the peptide into the secretory granules of neurotransmitter neurons in the pituitary gland (Glembotski, 1982; Chappell *et al.*, 1986).

Histone acetylation

Background information can be found in Section 6.6.4.

The DNA in cell nuclei does not exist in the 'naked' state – rather it is compacted into chromatin by winding around specific DNA-binding proteins called histones. The fundamental repeating unit of chromatin is the nucleosome. The organization of chromatin into nucleosomes is an essential feature in the regulation of gene transcription – the step in protein synthesis in which messenger RNA is synthesized from DNA.

It is necessary to control gene transcription so that only those proteins needed by a particular cell for a specific purpose are synthesized. When a protein is not needed, nucleosomes prevent transcription by impeding the access of factors required to initiate and regulate this process. When protein synthesis is required, changes in cell physiology cause a partial and localized alteration of chromatin structure (chromatin remodelling) in a manner that permits the binding of initiating and regulatory factors. One important chromatin remodelling system involves the enzyme-catalysed acetylation/deacetylation of core histones. Histone acetylation, which results in activation of transcription, requires acetyl-CoA as the acetyl donor (see Fig. 6.14).

α-Tubulin acetylation

Microtubules are constituents of the cytoskeleton and are composed of polymerized α- and β-tubulin dimers (Section 3.1.1). A subset of the α-tubulin is modified, like the histones, by post-translational acetylation of the ε-amino group of specific lysine residues. In contrast to histone acetylation, the acetylation of α-tubulin stabilizes the polymeric structure of the

microtubule; deacetylation is coupled to depolymerization (Plesofsky-Vig & Brambl, 1988).

Acylation of G proteins

Background information can be found in Section 3.7.5.

The biological activity of peptide hormones is mediated by second messengers such as cyclic AMP whose formation is triggered by the action of a G protein upon an effector enzyme. The reversible translocation of the G protein α-subunit between the plasma membrane and the cytoplasm is facilitated by the detachment and re-attachment of a palmitate group. Coenzyme A is required as the palmitate donor when Gα is palmitoylated by palmitoyl transferase (see Fig. 3.29).

The α-subunit of the G_i family of G proteins is further modified by the covalent attachment of myristic acid, which takes place during or immediately after translation. This modification is usually irreversible and therefore an unlikely target for regulation. Myristoylation promotes membrane attachment of the α subunit by increasing its affinity for membrane-bound βγ subunits; it also facilitates productive interaction with adenylate cyclase (Wilson & Bourne, 1995).

Farnesylation of rhodopsin kinase

Rhodopsin kinase, the enzyme which phosphorylates the photon-stimulated receptor rhodopsin and desensitizes the visual signal, is translocated from the cytosol to the rod outer segment membrane upon light exposure. This light-induced translocation is facilitated by farnesylation of the enzyme's CAAX motif (Inglese *et al.*, 1992). The synthesis of farnesol (an isoprenyl compound) requires CoA.

15.7 Deficiency in animals and humans

15.7.1 Animals

Pantothenic acid deficiency has been induced experimentally in many species of animals and birds by feeding diets containing low levels of the vitamin. The wide range of deficiency signs, histopathological abnormalities and metabolic changes indicate disorders of the nervous system, reproductive system, gastrointestinal tract and immune system. Immune defects in deficient animals have been attributed primarily to a block in the secretion of newly synthesized proteins out of the cell, resulting in their accumulation in the smooth endoplasmic reticulum (Axelrod, 1971). Rodents are particularly prone to necrosis and haemorrhage of the adrenal glands with consequent impairment of adrenal endocrine function. In young animals, the earliest sign of deficiency is a decline in the rate of growth. Distinctive visible signs are depigmentation of fur in rats and mice, and rough plumage and exudative lesions around the beak and eyelids of chickens. 'Goose-stepping' of the hind legs in pigs and ataxia in chicks are associated with demyelination of the motor neurons.

15.7.2 Humans

Human pantothenic acid deficiency has been carefully studied in healthy male volunteers given an emulsified artificial diet by stomach tube. In one study (Hodges *et al.*, 1958), two subjects received the basic diet devoid of pantothenic acid, a second pair received the same diet with added antagonist (omega-methyl pantothenic acid), and a third pair (the controls) received the diet supplemented with pantothenic acid. After about 4 weeks, subjects receiving the antagonist and those in the deficient group began to show similar symptoms of illness. Clinical observations were irritability, restlessness, drowsiness, insomnia, impaired motor co-ordination, and neurological manifestations such as numbness and 'burning feet' syndrome. The most persistent and troublesome symptoms were fatigue, headache and the sensation of weakness. Among the laboratory tests, the loss of eosinopenic response to adrenocorticotropic hormone indicated adrenocortical insufficiency.

15.8 Dietary intake

A Recommended Dietary Allowance (RDA) for a nutrient is derived from an Estimated Average Requirement (EAR), which is an estimate of the intake at which the risk of inadequacy to an individual is 50%. In the case of pantothenic acid, no data have been found on which to base an EAR, and an Adequate Intake (AI) is used instead of an RDA in the USA. The AI for infants up to 12 months old (1.7–1.8 mg per day) reflects the observed mean intake of breast-fed infants. The AI for

children aged 1 to 3 years (2 mg per day) is extrapolated from adult values. The AIs for children aged 4 to 13 years (3–4 mg per day), and adolescents and adults of both sexes (5 mg per day) are based on pantothenic acid intake sufficient to replace urinary excretion. AIs for women during pregnancy and lactation are 6 mg per day and 7 mg per day, respectively (Institute of Medicine, 1998).

There are no known toxic effects of oral pantothenic acid in humans or animals.

Further reading

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