Chapter 41

Niacin (B_3) and Pantothenic Acid (B_5)

Overview

- Niacin is a component of NAD^+ and $NADP^+$.
- Dietary nicotinamide, niacin, and Trp can all give rise to NAD^+.
- The Trp content of some food sources may be quantitatively more important in generating NMN, and thus NAD^+, than niacin itself.
- Coenzymes generated from niacin are best associated with dehydrogenase reactions.
- Niacin deficiency can result in pellagra.
- Pantothenic acid gives rise to two coenzymes, 4-phosphopantetheine and coenzyme A (i.e., CoA.SH).
- 4-Phosphopantetheine is a prosthetic group for acyl carrier protein, which participates in fatty acid biosynthesis.
- The reactive thiol (-SH) group of CoA.SH serves as a carrier (and activator) of acyl groups, most notably in degradative energy-yielding pathways.
- Lipoic acid is a B-complex vitamin whose only known function is to participate in the oxidative decarboxylations of a-ketoacids.

Niacin (Vitamin B_3)

This water-soluble vitamin is a component of the most central electron carrier substances in living cells, the **nicotinamide adenine dinucleotides** (i.e., **NAD^+/NADH**, and **$NADP^+$/NADPH**; see Chapter 18), and therefore functions in several important metabolic pathways (e.g., the **Embden Meyerhoff pathway** (**EMP**), the **hexose monophosphate shunt** (**HMS**), the **tricarboxylic acid** (**TCA**) **cycle**, **oxidative phosphorylation**, and **fatty acid biosynthesis** and **oxidation**). These electron carriers play a widespread role in many **dehydrogenase enzyme reactions** occurring in both the cytosol and within mitochondria. Generally, **NAD^+-linked dehydrogenases** catalyze redox reactions in **oxidative** pathways, whereas **$NADP^+$-linked dehydrogenases** (or reductases) are found in pathways concerned with **reductive biosynthesis**. The nicotinamide adenine dinucleotides are not tightly bound to their respective enzymes, and are therefore considered by some as true substrates (although they are most commonly referred to as **coenzymes**).

Dietary **nicotinamide**, **niacin** (**nicotinate**), and **tryptophan** (**Trp**) can all give rise to **nicotinate mononucleotide** (**NMN**), a precursor to both **NAD^+** and **$NADP^+$**, by enzymes present in most cells (**Fig. 41-1**). Dietary nicotinamide, which is naturally present in most plant and animal foods, must first undergo deamidation to nicotinate (which is added to many animal pet foods and complete feeds). This compound is then converted to **desamido-NAD^+** by reaction

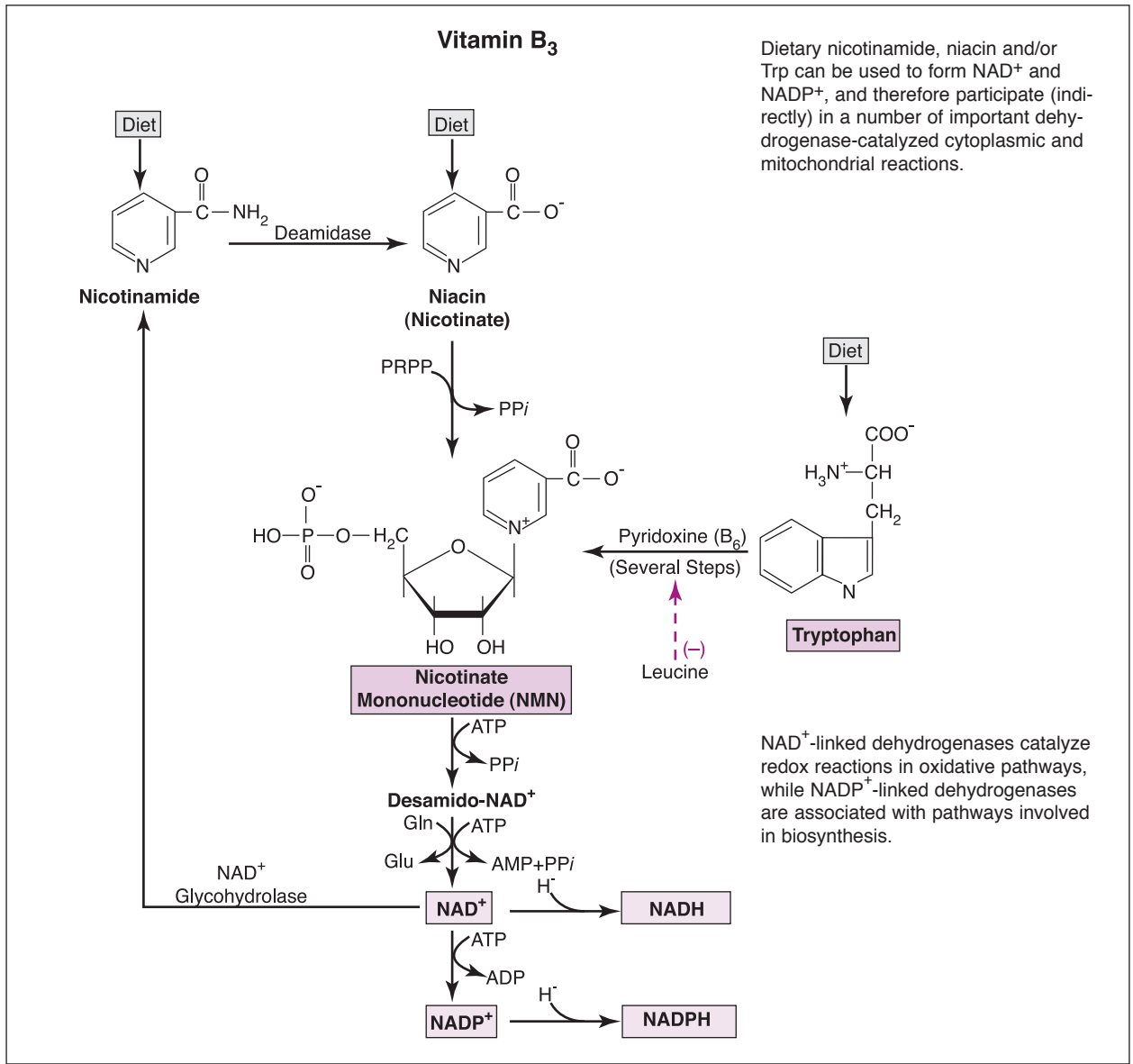

Figure 41-1

first with **5-phosphoribosyl-1-pyrophosphate** (**PRPP**), forming NMN, and then by adenylylation with ATP. The amido group of glutamine (Gln) then contributes to form the coenzyme **NAD**$^+$, which may be further phosphorylated to form **NADP**$^+$ (see Chapter 18).

As indicated above, NMN is also produced from the **essential** amino acid **Trp**, and although only about 1/60th of dietary Trp is normally utilized in this manner, this amount may increase 3-fold with pregnancy. It should be noted that the Trp content of some food sources may be quantitatively more important in generating NMN, and thus NAD$^+$, than niacin itself. For example, cow's milk normally has about 11 "niacin equivalents" in its Trp content (i.e., amount of Trp/60), yet only one niacin equivalent in its niacin content (an 11:1 ratio). For beef this ratio is about 21:2, eggs 19:1, wheat flour 5:2, yet for corn it is about 2:5. Additionally, **pyridoxal phosphate** (the active form of vitamin B_6; see Chapter 42) is needed to convert **Trp** to **NMN**. Therefore, in some dietary situations, a **vitamin B_6 deficiency** may lead to a **deficiency** of **NMN**.

Excess dietary **leucine** (e.g., from sorghum) has also been reported to contribute to niacin deficiency by inhibiting the key enzyme that converts **Trp** to **NMN**. Other conditions leading to symptoms of niacin deficiency include administration of drugs which divert **Trp** toward **serotonin** (**5-hydroxy-tryptamine**) formation, and **Hartnup syndrome**, in which Trp absorption is impaired in both the intestinal tract and the kidneys. Proximal renal tubular epithelial cells and mucosal cells in the jejunum contain similar transport proteins that couple the downhill transport of Na^+ into cells with the co-transport of amino acids (see Chapter 7). Some of these transporters are specific for the nonpolar, neutral amino acids like Trp, others for the basic and acidic amino acids, and still others for glycine and the imino acid proline (see Chapter 2). Patients with this disorder (as judged from high concentrations of neutral amino acids in urine) are much more likely to have symptoms if they also have poor diets. A patient with a high intake of niacin would be less likely to be symptomatic, and one with a high-protein diet would compensate somewhat for the loss of Trp by increasing absorption of this amino acid in dipeptides and tripeptides (see Chapter 7).

Niacin deficiency results in weakness (lassitude), indigestion and inappetence, and later in the classic signs of "**pellagra**" (i.e., the "**3 Ds**" – **dermatitis, diarrhea, and dementia** –). In addition, some animals reportedly exhibit vomiting with evidence of inflamed mucus membranes. The dementia is said to progress to irritability, sleeplessness, confusion, and eventually delirium and catatonia.

Like most of the other B-complex vitamins, niacin stores in the body are minimal, and it appears to be nontoxic in large doses. Large pharmacologic doses have been used to help lower serum cholesterol. It reportedly reduces the flux of fatty acids from adipose tissue, which leads to less formation of cholesterol-bearing lipoproteins (VLDL —> IDL —> LDL; see Chapters 65 and 67).

Pantothenic Acid (Vitamin B_5)

This water-soluble vitamin, a constituent of pet foods, plants, and animal tissues, has been shown to be an essential **growth factor** for several different species (e.g., chicks, rats, and others). It is found largely as part of two coenzymes, **4-phosphopantetheine** and **coenzyme A** (**CoA** or **CoA.SH**; **Fig. 41-2**). It is customary to abbreviate the structure of the free (i.e., reduced) CoA as CoA.SH, in which the reactive **thiol** (sulphydryl or -SH) group of the coenzyme is designated. It is this thiol group which esterifies with carboxylic acids to form **acyl-CoA** compounds, which are, therefore, **thioesters**:

$CoA.SH + R\text{-}COOH \longrightarrow R\text{-}CO.SCoA + H_2O$

An acyl group often linked to CoA is the acetyl unit, thus forming acetyl-CoA. Acyl-CoA compounds are important in both catabolism, as in the oxidation of fatty acids, and in anabolism, as in the synthesis of membrane lipids. The exception to the presence of these coenzyme derivatives in animals appears to be blood plasma, where this vitamin is found primarily as pantothenic acid.

Although little is known about its absorption and metabolism, the fact that plasma contains pantothenic acid in non-coenzyme form indicates that the vitamin B_5 coenzymes in food are broken down before or during intestinal absorption. Pantothenic acid, like other water-soluble vitamins, is freely filtered by the kidneys and excreted into urine.

The important coenzyme actions of intracellular pantothenic acid derivatives are numerous, and quite well documented. Thioesters of **CoA.SH** play a central role in pathways of **energy metabolism**, and **4-phosphopantetheine** is an important prosthetic group in **acyl carrier**

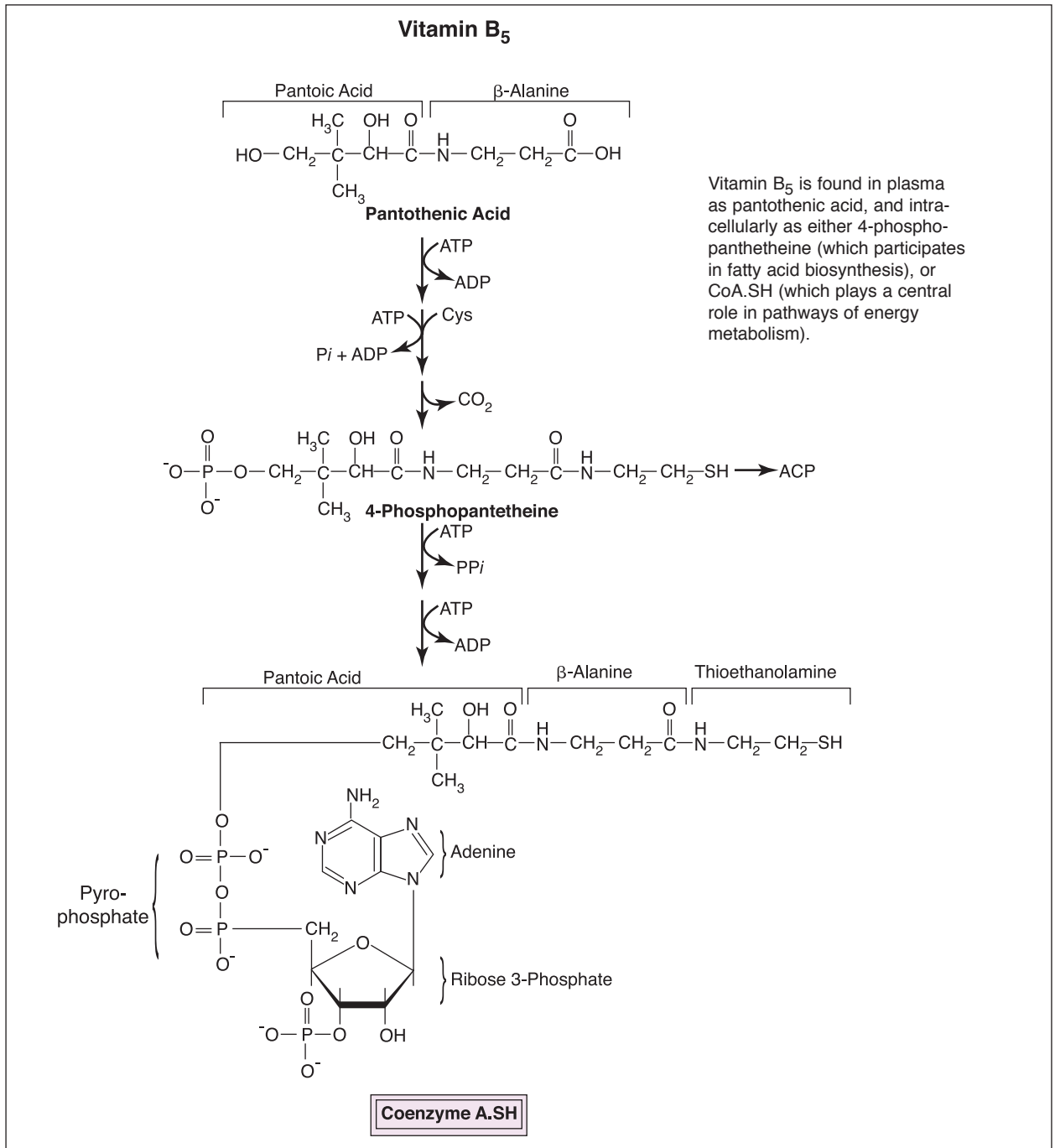

Figure 41-2

protein (**ACP**), which participates in reactions concerned with fatty acid biosynthesis (see Chapter 56). Some examples of reactions involving these pantothenic acid derivatives are as follows:

- The **first step** in the **TCA cycle** (transfer of an acetyl group from acetyl-CoA to oxaloacetate, thus forming citrate; see Chapter 34).
- The **fifth step** in the **TCA cycle** (conversion of succinyl-CoA to succinate; see Chapter 34).
- **Activation of long-chain fatty acids** in the cytoplasm and **propionate** in mitochondria (by appropriate acyl-CoA synthetases; see Chapter 55).
- **Mitochondrial β-oxidation of fatty acids** (recipient of acetyl units removed from the fatty acid chain; carrier of the fatty acid moiety; see Chapter 55).

- **Cytoplasmic synthesis of cholesterol** from 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA; see Chapter 61).
- **Mitochondrial synthesis of ketone bodies** from HMG-CoA (see Chapter 71).
- **Acetylcholine biosynthesis** (see Chapter 57).
- **Porphyrin biosynthesis** (conversion of succinyl-CoA + glycine to Δ-aminolevulinate; see Chapter 32).
- **Fatty acid or acetate transfer** to polypeptides, including some enzymes, receptors, and hormones.

Pantothenic acid deficiency is considered to be rare among domestic animal species, except as an accompaniment of general malnutrition. When deliberately induced, deficiency symptoms include vomiting, malaise, and abdominal distress. Another deficiency symptom reported in humans is burning cramps in the extremities (i.e., "burning foot syndrome").

Lipoic acid

Lipoic acid is another B-complex vitamin, whose only known function is to participate in the **oxidative decarboxylations** of α-ketoacids, principally conversion of pyruvate to acetyl-CoA, and α-ketoglutarate to succinyl-CoA, two similar dehydrogenase complexes of the TCA cycle. However, it has not been shown to be essential as a dietary component of animals. As such minute amounts are needed, and because some lower organisms do require it as a growth factor, the question of whether it is produced in the tissues of higher organisms, or is acquired in sufficient quantities through the diet, remains unanswered. Lipoic acid (structure not shown), like thiamin and biotin, contains sulfur, and has been isolated from liver and yeast. It is covalently linked to the enzymes that require it through a peptide bond with the terminal side-chain amino group of lysine.

OBJECTIVES

- Contrast the different types of dehydrogenase reactions using NAD^+ as a coenzyme, to those using $NADP^+$ as a coenzyme.
- Trace biochemical steps in the conversion of dietary nicotinamide and/or nicotinate to NAD^+.
- Explain how dietary pyridoxine (B_6), Leu and/or Trp can affect physiologic supplies of NMN, and thus NAD^+.
- Recognize what is meant by a "niacin equivalent."
- Explain the causes and symptoms of Hartnup syndrome and pellagra.
- Identify the coenzyme forms of pantothenate.
- Describe reactions in the TCA cycle that are dependent upon a coenzyme form of pantothenate.
- Show how vitamin B_5 participates in both fatty acid β-oxidation and fatty acid biosynthesis (see Chapters 55 & 56).
- Indicate how CoA.SH assists in the incorporation of a volatile fatty acid (propionate) into hepatic gluconeogenesis (see Chapter 37).
- Identify vitamin B_5-dependent reactions catalyzed by -ALA synthase, HMG-CoA reductase and HMG-CoA lyase (see Chapters 32, 61 & 71).
- Identify two decarboxylation reactions of the TCA cycle that require lipoic acid.

QUESTIONS

1. Which one of the following amino acids is used in the biosynthesis of nicotinate mononucleotide (NMN)?

a. Alanine
b. Tyrosine
c. Leucine
d. Tryptophan
e. Glycine

2. A deficiency of which one of the following B-complex vitamins would make it more difficult to convert Trp to NMN, and therefore potentiate a niacin deficiency?

a. Pyridoxine
b. Folic acid

c. Biotin
d. Riboflavin
e. Thiamin

3. Niacin deficiency is best associated with:
a. Scurvy.
b. Beriberi.
c. Adrenal insufficiency.
d. Pellagra.
e. Megaloblastic anemia.

4. Which of the following enzymes are best associated with niacin (vitamin B_3)?
a. Kinases
b. Carboxylases
c. Dehydrogenases
d. Isomerases
e. Phosphatases

5. 4-Phosphopantetheine is:
a. A prosthetic group for acyl carrier protein.
b. Synthesized from niacin.
c. Used by animals to synthesize pantothenic acid (vitamin B_5).
d. Also known as coenzyme A.
e. A natural product of plant, but not animal metabolism.

6. Coenzyme A.SH is associated with all of the following, EXCEPT:
a. Porphyrin biosynthesis.
b. Ketone body synthesis.
c. Cholesterol synthesis.
d. Mitochondrial β-oxidation of fatty acids.
e. Cytoplasmic glycogen synthesis.

7. Acyl-CoA compounds are properly referred to as:
a. Porphyrins.
b. Thioesters.
c. Fatty acids.
d. Vitamins.
e. Nicotinamides.

8. Lipoic acid is:
a. A fat-soluble vitamin.
b. An essential dietary component of animals.
c. A B-complex vitamin.
d. A short-chain, volatile fatty acid produced by rumen microbes.
e. An unsaturated fatty acid found in the 2-position of numerous membrane-bound phospholipids.

9. Approximately what amount of the dietary Trp intake is used for NMN synthesis?
a. $1/6^{th}$
b. $1/60^{th}$
c. $1/600^{th}$
d. $1/6{,}000^{th}$
e. $1/60{,}000^{th}$

10. Which TCA cycle enzymes are associated with pantothenate?
a. Malate dehydrogenase and α-KG$^{=}$ dehydrogenase
b. Succinate dehydrogenase and aconitase
c. Isocitrate dehydrogenase and fumarase
d. Succinate thiokinase and citrate synthase
e. None of the above

11. Pantothenic acid:
a. Functions in the ETC in its coenzyme form (CoQ).
b. Is filtered by the kidneys and excreted in urine.
c. Is found in its active coenzyme form in plasma.
d. Is a fat-soluble vitamin
e. Like carbohydrates, lacks nitrogen.

12. Cholesterol biosynthesis from acetyl-CoA requires pantothenic acid (vitamin B_5), but not niacin (vitamin B_3):
a. True
b. False

13. The oxidative decarboxylation of pyruvate to acetyl-CoA requires:
a. ATP, CO_2, biotin and pyruvate carboxylase.
b. Malic enzyme, NADPH, ATP and lipoic acid.
c. CO_2, vitamin B_6, NADH and biotin.
d. Thiamin, lipoic acid, niacin, pantothenic acid and pyruvate dehydrogenase.

ANSWERS

1. d
2. a
3. d
4. c
5. a
6. e
7. b
8. c
9. b
10. d
11. b
12. b
13. d