Biotin[1,2]

In mammals, biotin serves as a covalently bound coenzyme for 5 carboxylases: acetyl-CoA carboxylases 1 and 2, propionyl-CoA carboxylase (PCC),[5] 3-methylcrotonyl-CoA carboxylase (MCC), and pyruvate carboxylase (1). Acetyl-CoA carboxylase 1 localizes in the cytoplasm, where it catalyzes the binding of bicarbonate to acetyl-CoA in a key step in fatty acid synthesis. All other carboxylases localize in mitochondria. PCC catalyzes an essential step in the metabolism of propionyl-CoA, which originates in the catabolism of odd-chain fatty acids and some other nutrients. MCC catalyzes a key step in the metabolism of the amino acid leucine. Pyruvate carboxylase catalyzes the conversion of pyruvate to oxaloacetate, which is a key step in gluconeogenesis.

Holocarboxylase synthetase (HLCS) catalyzes the binding of biotin to all 5 carboxylases and, therefore, plays a pivotal role in biotin-dependent metabolic pathways (1). In addition, HLCS participates in gene regulation at the chromatin level, as discussed in Recent Research. Consistent with the important roles of HLCS in biotin metabolism, no living HLCS null individual has ever been reported, suggesting embryonic lethality. Mutations have been identified and characterized in the human *HLCS* gene; these mutations cause a substantial decrease in HLCS activity and metabolic abnormalities. Some mutations respond well to pharmacological doses of biotin if diagnosed early.

Biotinidase catalyzes the release of biotin from breakdown products of carboxylases and, therefore, plays a crucial role in biotin recycling (1). Mutations in the *biotinidase* gene impair the recycling of biotin and lead to a substantial urinary loss of biotin in form of biotinylated peptides. Afflicted patients are treated with pharmacological doses of biotin to compensate for the urinary loss of biotin.

Biotin affects gene regulation by "classic" signaling pathways such as cyclic guanosine monophosphate, nuclear factor-κB, Sp1 and Sp3, nitric oxide, and receptor tyrosine kinases, by the intermediate biotinyl-5′-adenosyl monophosphate, and at the posttranscriptional level (1).

Deficiencies: Signs of frank biotin deficiency may be observed in individuals with deficiencies in biotin, HLCS, and biotinidase and in individuals consuming large amounts of raw egg white; the biotin-binding protein avidin in raw egg white causes a substantial decrease in the bioavailability of biotin (1). A rare biotin transporter defect has been identified that may also cause severe biotin deficiency. Clinical findings of frank biotin deficiency include periorificial dermatitis; conjunctivitis; alopecia; ataxia; hypotonia; ketolactic acidosis/organic aciduria; seizures; skin infection; thinning hair; skin rashes around the eyes, nose, and mouth; impaired immune function; and developmental delay in infants and children.

Biotin status is typically assessed by quantifying the urinary excretion of biotin and its major metabolites (~120 nmoles/d), the activity of PCC or MCC in lymphocytes, and the abundance of biotinylated carboxylases in cell extracts (1). Biotin deficiency causes low activity of MCC, thereby shunting metabolites from leucine metabolism to alternative pathways. Low MCC activity causes increased urinary excretion of 3-hydroxyisovaleric acid and its carnityl conjugate, which is used to diagnose biotin deficiency.

Evidence suggests that biotin catabolism is accelerated in pregnancy and that about half of pregnant women in the United States are marginally biotin deficient (1). Likewise, biotin deficiency might be encountered in smokers, users of certain anticonvulsants, and after consumption of pharmacological doses of lipoic acid.

Intake recommendations: The human requirement of biotin is not known and, therefore, recommendations for adequate intake (AI) are based on the average intake of biotin in an apparently healthy population (2,3). The AI for biotin is 30 μg/d in men, women, and pregnant women 19 y and older and increases to 35 μg/d for lactating women. The AI is 5 μg/d for infants 0–6 mo of age, 6 μg/d for infants 7–12 mo of age, 8 μg/d for children 1–3 y of age, 12 μg/d for children 4–8 y of age, 20 μg/d for young adults 9–13 y of age, and 25 μg/d for young adults 14–18 y of age. These recommendations need to be met with some uncertainty because the content of biotin in most foods was not analyzed by chemically specific assays (see Food Sources).

Food sources: Biotin is widely distributed in foods (1). Foods relatively rich in biotin include egg yolk, liver, whole cereals, and some vegetables. The dietary biotin intake in Western populations is ~35–70 μg/d (143–287 nmoles/d). The majority of biotin analyses in foods were conducted by using microbial growth assays and other assays that are not chemically specific for biotin (as opposed to biotin precursors and catabolites). Infants consuming 800 mL of mature breast milk per day

ingest ~6 μg (24 nmoles) of biotin. It is unknown whether biotin synthesis by gut microorganisms contributes meaningful quantities of bioavailable biotin.

The majority of biotin in foods is protein bound and requires hydrolytic release by biotinidase before absorption (1). Evidence suggests that dietary biotin is 100% bioavailable.

Clinical uses: Pharmacological doses of biotin (several milligrams per day) are being given to individuals with mutations in genes coding for HLCS and biotinidase. To date, evidence is insufficient to justify the use of pharmacological doses of biotin for other reasons.

Toxicity: No tolerable upper intake has been specified in the dietary reference intakes (2,3). Based on the observation that HLCS and biotinidase deficiency patients are treated with pharmacological doses of biotin for their entire life with no apparent signs of toxicity, one can assume with reasonable confidence that the toxicity of biotin is very low (1).

Recent research: Unambiguous evidence suggests that HLCS has catalytic activity to mediate the binding of biotin to histones H3 and H4 and that histone biotinylation marks are enriched in repressed loci and repeat regions (1,4). Low abundance of histone biotinylation marks in biotin and HLCS-deficient cells and whole organisms coincides with both derepression of retrotransposons and impaired genome stability. However, <0.001% of histones H3 and H4 are biotinylated, triggering questions as to how a low-abundance epigenetic mark may have meaningful effects on gene regulation and genome stability. Recent lines of evidence suggest that the roles of HLCS go beyond that of a protein biotinyl ligase and include the participation of HLCS in forming gene repression multiprotein complexes in human chromatin. The biotin-dependent expression of HLCS and the subsequent repression of retrotransposons by an HLCS/protein complex might be the long-sought mechanism linking biotin deficiency with birth defects.

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[5]Abbreviations used: AI, adequate intake; HLCS, holocarboxylase synthetase; MCC, 3-methylcrotonyl-CoA carboxylase; PCC, propionyl-CoA carboxylase.

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