**Monograph**

Biotin

Introduction

Biotin is a water-soluble B vitamin that is an essential cofactor for four carboxylase enzymes, each of which catalyzes an essential step in intermediary metabolism. Because humans and other mammals cannot synthesize biotin, it must be derived from dietary sources and *de novo* synthesis by intestinal bacteria. Biotin was originally recognized when rats fed protein derived from egg whites developed severe dermatitis, hair loss, and neuromuscular dysfunction. A growth factor found in liver, then called "Protective Factor X," cured the condition; this growth factor is now known as biotin. It was later discovered that uncooked egg whites contain a glycoprotein, avidin, that binds to biotin and prevents its absorption, whether biotin is from the diet or from intestinal bacterial synthesis.[1] Besides genetic inborn errors of metabolism, biotin deficiency can occur during extended parenteral nutrition, pregnancy, or long-term anticonvulsant therapy. Conditions that may benefit from biotin supplementation include dyslipidemia, brittle nails, diabetes, dermatitis, and candidiasis.
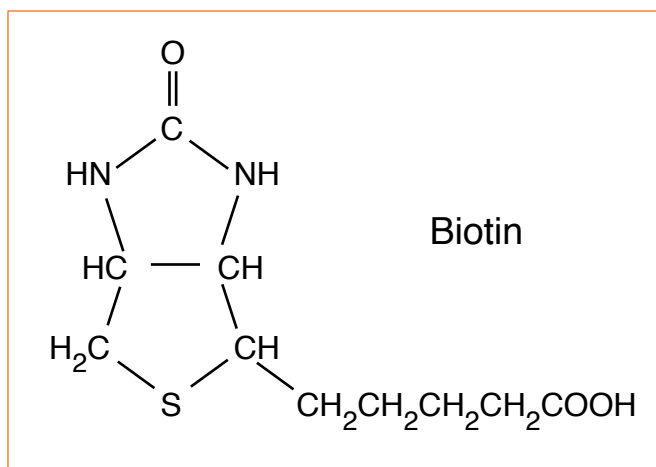
Biochemistry

The chemical structure of biotin, first elucidated in the early 1940s, is a bicyclic compound; one ring contains a ureido group (-N-CO-N-) and the other sulfur (a tetrahydrothiophene ring). Only one of eight possible stereoisomers of biotin is found in nature and is enzymatically active – d-(+)-biotin (or simply "D-biotin").

Pharmacokinetics

Oral biotin is completely absorbed, even at high, pharmacological doses. Urinary excretion of biotin and its metabolites is similar for intravenous dosing and oral supplementation at high doses, suggesting 100-percent bioavailability of orally administered biotin.[2] Percutaneous absorption of biotin from a biotin-containing ointment has been demonstrated in healthy subjects and patients with atopic dermatitis.[3]

Biotin is absorbed via a sodium-dependent, carrier-mediated system.[4] After transport from the intestines to the peripheral circulation, biotin is taken up by the liver and eventually crosses the blood-brain barrier into the central nervous system via a saturable system.[5] In healthy adults and children not receiving biotin supplementation, the kidneys clear biotin and creatinine in a ratio of approximately 0.4.[1] Specific systems for transport of biotin from mother to fetus[6-8] and from mother to infant via breastmilk,[9,10] have been described.

Mechanisms of Action

In humans, biotin is required as a prosthetic group for four major carboxylase enzymes involved in several critical metabolic pathways, including gluconeogenesis, fatty acid synthesis, and amino acid catabolism. All four carboxylase enzymes catalyze the incorporation of bicarbonate into a substrate as a carboxyl group. Three of these carboxylase enzymes are located in mitochondria; the fourth (acetyl-CoA carboxylase; ACC) is found in both cytosol and mitochondria. ACC catalyzes incorporation of bicarbonate into acetyl-CoA, and finally into malonyl CoA. Malonyl CoA

subsequently acts as a substrate for fatty acid synthesis, with the effect of elongating the fatty acid chain. Other carboxylases, decarboxylases, and a transcarboxylase are also dependent on biotin as an enzyme cofactor.

Recent research has illuminated several other mechanisms of action. Biotin at pharmacological doses (3.1 µM/day) to healthy adults resulted in decreased synthesis of cytokines (interleukin-1ß and interleukin-2) and decreased proliferation of peripheral blood mononuclear cells (PBMC) – a combination of T-cells, B-cells, and granulocytes.[11]

Biotin appears to exert an effect on gene transcription,[12] although research is in its infancy. Researchers have identified more than 2,000 biotin-dependent genes.[13] Biotin has been found to attach to histones, a process catalyzed by the enzymes holocarboxylase synthetase[14] and biotinidase.[15] This recent discovery provides one mechanism whereby biotin might regulate chromatin structures, gene expression, and DNA repair.[15]

Deficiency States

Biotin deficiency in humans is rare and generally associated with extended parenteral nutrition, consumption of large quantities of raw egg whites, severe malnutrition, or inborn errors of metabolism (e.g., biotinidase deficiency, multiple carboxylase deficiency). Studies of biotin status during pregnancy suggest marginal biotin deficiency, occurring in a significant number of otherwise normal pregnancies, may be teratogenic.[16] One study found 50 percent of pregnant women had increased urinary excretion of 3-hydroxyisovaleric acid (a reflection of biotin deficiency) that was reversed by supplementation of 300 mcg biotin for 14 days.[17] Individuals on long-term anticonvulsant therapy are also at high risk for a biotin deficiency (see Drug-Nutrient Interactions below). Signs and symptoms of severe biotin deficiency include erythematous skin lesions, vomiting, seizures, developmental delay, hypotonia, and ataxia.[18]

One study found 3-hydroxyisovaleric acid to be the most reliable urinary indicator of biotin deficiency; urinary 3-hydroxypropionic acid and methylcitric acid were not as reliable.[19] The most sensitive indicator of a biotin deficiency, reliably detecting even a marginal deficiency, appears to be measurement of lymphocyte propionyl-CoA carboxylase activity.[20]

Clinical Indications
Brittle Nails (Onychoschizia)

Although the mechanism is unknown, biotin supplementation appears to improve brittle nails. In an uncontrolled trial, 45 patients with brittle nails received oral supplementation of 2.5 mg biotin daily for 1.5-7 months. Ninety-one percent showed "definite improvement," exhibiting firmer, harder nails after an average of two months of treatment.[21] Another uncontrolled trial reported a 63-percent response rate to biotin supplementation for brittle nails.[22] In a controlled trial, women with brittle nails who took 2.5 mg biotin daily for 6-15 months had 25-percent increased nail thickness; nail splitting was also reduced.[23]

Dermatitis

Biotin deficiency can cause alopecia and a characteristic scaly, erythematous dermatitis distributed around body orifices. Candida albicans can often be cultured from the skin lesions. Reduced activity of the biotin-dependent carboxylases (particularly ACC) impairs fatty acid metabolism and probably plays an etiologic role in the dermatologic manifestations of biotin deficiency.[24] Dermatitis is a common feature in children with inherited biotinidase deficiency.[25] Seborrheic dermatitis in children with phenylketonuria has been associated with an impairment of biotin recycling.[26] However, although biotin deficiency can cause seborrheic dermatitis-like signs and symptoms, common infantile seborrheic dermatitis does not necessarily suggest biotin deficiency[27] or respond to biotin supplementation.[28] Further research is needed to demonstrate clinical efficacy of biotin supplements for non-deficiency related dermatitis.

Dyslipidemia

Animal[29,30] and human[31] data suggest poor biotin status adversely affects plasma lipid levels. In a double-blind trial, healthy volunteers were given 900 mcg biotin daily for 71 days.[32] Small, but statistically significant, positive changes in lipid profiles were observed for biotin-treated subjects, as well as an inverse association between biotin levels and total plasma lipids. Another study examined the effect of 15 mg biotin daily or placebo for 28 days on lipid, glucose, and insulin levels in type 2 diabetic and non-diabetic subjects.[33]

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Biotin resulted in significant decreases in triglycerides and very low-density lipoproteins (VLDL) in both diabetic and non-diabetic subjects compared to placebo. There were no significant differences in glucose, insulin, or total cholesterol in biotin-treated subjects compared to placebo.

Diabetes

It is thought biotin improves abnormal glucose metabolism by stimulating glucose-induced insulin secretion in pancreatic beta cells and by accelerating glycolysis in the liver and pancreas.[34] Biotin also enhances muscle insulin sensitivity by increasing guanylate cyclase activity.[35] Although impairment of carboxylase enzymes in diabetes has been hypothesized, researchers found no differences in the activity of three biotin-dependent carboxylase enzymes between diabetic and non-diabetic subjects.[36]

Administration of high-dose biotin improved glycemic control in several diabetic animal models.[37] A Japanese study found biotin levels were lower in patients with type 2 diabetes than healthy controls.[38] In this same study, oral supplementation of 3 mg biotin three times daily for one month lowered fasting glucose levels by 45 percent in type 2 diabetics for whom sulfonylureas were no longer effective; no effect was observed in subjects taking placebo. In another study, patients with type 1 diabetes given 16 mg biotin daily for one week experienced a 50-percent reduction in fasting glucose levels.[39] Biotin in high doses (10 mg/day intramuscularly for six weeks, followed by 5 mg/day orally for 64-130 weeks) was given to three diabetic patients with severe diabetic peripheral neuropathy.[40] Within eight weeks a marked improvement in paresthesias and muscle cramps occurred, along with a disappearance of restless legs syndrome. There is also preliminary evidence that intravenous biotin (50 mg post-dialysis) normalizes oral glucose tolerance tests in normoglycemic hemodialysis patients.[41]

A randomized, double-blind, placebo-controlled trial examined the effect of biotin and chromium picolinate in 43 poorly controlled type 2 diabetics (glucose during glucose tolerance test at two hours >200 mg/dL; glycosylated hemoglobin ≥7) on oral hypoglycemic agents.[42] Subjects were randomly assigned to take 2 mg biotin and 600 mcg chromium (as picolinate) or placebo once each morning for four weeks; prestudy oral hypoglycemic agents were continued. Significant reductions in glucose (area under the curve during a two-hour glucose tolerance test), fructosamine, triglycerides, and triglyceride/HDL cholesterol ratio were noted in the treatment group compared to placebo.

In another study, 10 type 2 diabetics and seven non-diabetics supplemented with 5 mg biotin three times daily exhibited no changes in glucose, insulin, or lipid levels after 28 days.[36]

Multiple Carboxylase Deficiency

Acquired biotin deficiency and the two known congenital disorders of biotin metabolism – biotinidase deficiency and holocarboxylase synthetase (HCS) deficiency – lead to a deficiency of the four biotin-dependent carboxylase enzymes (i.e., multiple carboxylase deficiency). The two inherited disorders of biotin metabolism, both discovered in the early 1980s, respond clinically and biochemically to oral biotin therapy. While 10 mg daily is usually sufficient to treat severe biotinidase deficiency, the optimal dose for patients with HCS deficiency is assessed on a case-by-case basis. If biotin therapy is initiated early and continued throughout life, the prognosis for both conditions is generally good. However, a delay in initiating therapy in biotinidase deficiency can cause irreversible neurological damage. In the case of HCS deficiency, some patients respond only partially, even at daily biotin doses up to 100 mg.[43]

Biotin-Responsive Basal Ganglia Disease

Biotin-responsive basal ganglia disease is a rare condition, described in at least 10 patients, that reportedly responds to biotin supplementation. The disease presents with subacute encephalopathy and multiple neurological symptoms,[44] and may be related to a defect in biotin transport across the blood-brain barrier.

Chronic Vaginal Candidiasis

A single case has been reported of a 38-year-old female carrier of biotinidase deficiency who presented with a 14-month history of persistent vaginal candidiasis, despite therapy.[45] After three months of biotin supplementation, her symptoms resolved completely. The authors suggest, since one in every 123 people is thought to be a carrier of biotinidase deficiency, other women with chronic vaginal candidiasis might respond to biotin administration.

Sudden Infant Death Syndrome (SIDS)

Animal studies first suggested biotin deficiency might be a contributing factor in SIDS. Subsequently, autopsies indicated biotin levels in livers of 204 SIDS infants were significantly lower than those in livers of similar-age infants who had died of known causes.[46] No research has explored the effects of maternal or infant biotin supplementation on SIDS.

Uremic Neurological Disorders

Encephalopathy and peripheral neuropathy commonly develop in uremic patients on hemodialysis. Nine such patients, treated with 10 mg oral biotin daily, experienced marked improvements within three months; the improvement was maintained in six of the nine patients in the ensuing 15-25 months of follow-up (the other three died of renal failure).[47] Hemodialysis is thought to deplete biotin, which may in turn be responsible for neurological symptoms that accompany severe uremia.

Veterinary Medicine: Hoof Health and Milk Yield

Biotin is used in veterinary medicine as a treatment for hoof disorders. Hereford cows given 10 mg biotin daily demonstrated increased claw hardness and fewer had vertical fissures (15%) compared to unsupplemented cows (33%).[48] In a double-blind trial, supplementing 40 mg biotin/day or placebo for 50 days to 24 dairy cows with mild sole ulcers resulted in better horn structure in deep epidermal layers in biotin-supplemented cows compared to placebo.[49] In a randomized study, 20 mg biotin daily to Holstein cows resulted in significant increases in milk yield compared to unsupplemented cows. Addition of a B-vitamin blend or increased biotin dosage (40 mg/day) did not offer additional yield.[50]

Drug-Nutrient Interactions

Several studies have shown long-term therapy with anticonvulsants (i.e., phenobarbital, phenytoin, carbamazepine, and primidone) depletes plasma concentrations of biotin[51-54] or inhibits biotinidase activity (valproic acid).[55] Isotretinoin (13-cis-retinoic acid, commonly used for acne) impairs biotinidase activity, but the effect on biotin levels is unclear.[56] Since biotin

is known to affect glucose regulation, theoretical drug interactions exist with insulin or oral glucose-lowering drugs.

Side Effects and Toxicity

No biotin toxicity has been reported in individuals supplemented with as much as 200 mg orally or 20 mg intravenously per day.[1]

Dosage

Therapeutic dosages range widely; for example, 2.5 mg daily has been used successfully for brittle nails, 15 mg daily for improving lipid levels (particularly triglycerides), and 9-16 mg daily to decrease glucose levels in diabetes. Both oral (uremic neurological syndrome) and intramuscular (diabetic neuropathy) doses of 10 mg daily have been used successfully to treat peripheral neuropathy. An optimal daily biotin intake for healthy adults remains speculative.[1]

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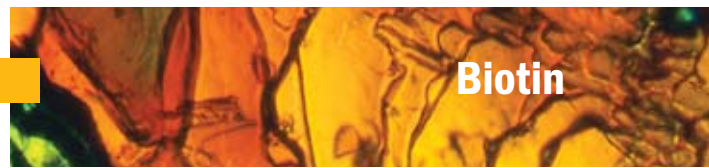
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