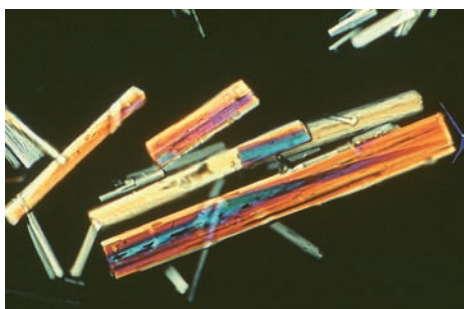


Biotin



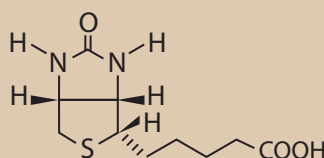
Biotin crystals in polarised light

Synonyms

Vitamin H ("**H**aar und **H**aut", German words for "hair and skin"), vitamin B₈ and co-enzyme R.

Chemistry

Biotin has a bicyclic ring structure. One ring contains a ureido group and the other contains a heterocyclic sulphur atom and a valeric acid side-group. (Hexahydro-2-oxo-1H-thieno [3,4-d]imidazole-4-pentanoic acid). Biologically active analogues: biocytin (ε-N-biotinyl-L-lysine), oxybiotin (S substituted with O).



Molecular formula of biotin

Introduction

Biotin is a colorless, water-soluble member of the B-complex group of vitamins. Although biotin was discovered already in 1901 as a special growth factor for yeast, it took nearly forty years of research to establish biotin as a vitamin. Due to its beneficial effects for hair, skin and nails, biotin is also known as the “beauty vitamin”. There are eight different forms of biotin, but only one of them – D-biotin – occurs naturally and has full vitamin activity. Biotin can only be synthesised by bacteria, moulds, yeasts, algae, and by certain plant species.

Functions

Biotin plays a key role in the metabolism of lipids, proteins and carbohydrates. It acts as a critical coenzyme of four carboxylases (enzymes):

- acetyl-CoA carboxylase (involved in the synthesis of fatty acids from acetate)
- propionyl-CoA carboxylase (involved in gluconeogenesis, i.e. the generation of glucose from lactate, glycerol, and amino acids)
- β -methylcrotonyl-CoA carboxylase (necessary for the metabolism of leucin, an essential amino acid)
- pyruvate carboxylase (involved in energy metabolism, necessary for the metabolism of amino acids, cholesterol, and odd chain fatty acids)

Biotin also plays a special role in enabling the body to use blood glucose as a major source of energy for body fluids. Furthermore, biotin may have a role in DNA replication and transcription arising from its interaction with nuclear histone proteins. It owes its reputation as the “beauty vitamin” to the fact that it activates protein/amino acid metabolism in the hair roots and fingernail cells.

Main functions in a nutshell:

- Synthesis of fatty acids, amino acids and glucose
- Energy metabolism
- Excretion of by-products from protein metabolism
- Maintenance of healthy hair, toenails and fingernails

Dietary sources

Biotin is widely distributed in most foods but at very low levels compared to other water-soluble vitamins. It is found in free and protein-bound forms in foods. Its richest sources are yeast, liver and kidney. Egg yolk, soybeans, nuts and cereals are also good sources. 100 g of liver contains approximately 100 μ g biotin, whereas most other meats, vegetables and fruits only contain approximately 1 μ g biotin /100 g. In animal experiments, biotin bioavailability has been shown to vary considerably (5%-62%), and in cereals it appears to be lower.

Biotin content of foods

Food	Biotin (μ g/100g)
Brewer's yeast	115
Beef liver	100
Soya beans	60
Wheat bran	45
Peanuts	35
Egg	25
White mushrooms	16
Spinach	6.9
Bananas	6
Strawberries	4
Whole wheat bread	2
Asparagus	2

(Souci, Fachmann, Kraut)

Biotin-producing microorganisms exist in the large intestine, but the extent and significance of this enter-

al synthesis in the overall biotin turnover is difficult to calculate and thus remains a subject of controversy.

Absorption and body stores

In most foodstuffs biotin is bound to proteins from which it is released in the intestine by protein hydrolysis and a specific enzyme, biotinidase. Biotin is then absorbed unchanged in the upper part of the small intestine by an electron-neutral sodium (Na^+) gradient dependent carrier-mediated process and also by slow passive diffusion. The carrier is regulated by the availability of biotin, with up-regulation of the number of transporter molecules when biotin is deficient. The colon is also able to absorb biotin via an analogue transport mechanism. Once absorbed, biotin is distributed to all tissues. The presence of a specific biotin carrier protein in plasma is not yet conclusive. The liver and retinal tissues are the main storage places. Biotin metabolites are not active as vitamins and are excreted in the urine. Remarkable amounts of biotin appear in the faeces deriving from colonic bacteria.

Measurement

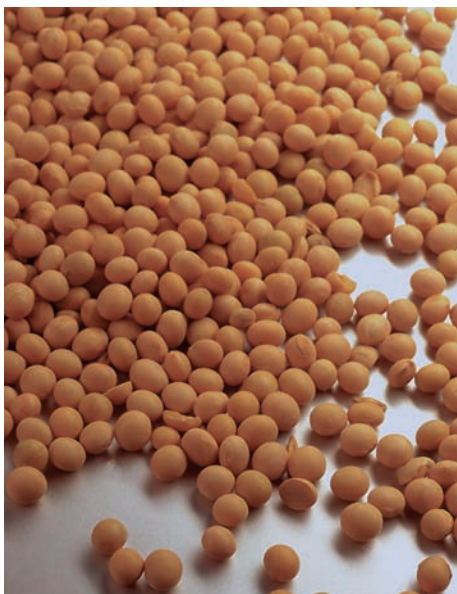
The body status of biotin can be determined by measuring its activity and/or activation of biotin dependent enzymes – predominately carboxylases – by added biotin. More convenient methods are direct determination of biotin in plasma or serum by microbiological methods or avidin binding assays, or determination of biotin excretion and 3-hydroisovaleric acid in urine. Measurement of biotin in plasma is not a reliable indicator of nutritional

status, because reported levels for biotin in the blood vary widely. Thus, a low plasma biotin concentration is not a sensitive indicator of inadequate intake.

Usual serum concentrations = 100 - 400 pmol/L.

Stability

Biotin is relatively stable when heated and so is not easily destroyed in the ordinary processes of cooking but it will leach into cooking water. Processing of food, e.g. canning, causes a moderate reduction in biotin content.



Groups at risk of deficiency

- patients maintained on total parenteral nutrition
- people who eat large amounts of raw egg white
- haemodialysis patients
- diabetes mellitus
- individuals receiving some forms of long-term anticonvulsant therapy
- individuals with biotinidase deficiency or holocarboxylase synthetase (HCS) deficiency (genetic defects)
- patients with malabsorption, including short-gut syndrome
- pregnancy may be associated with marginal biotin deficiency

Interactions

Negative interactions

Raw egg whites contain avidin, a glycoprotein that strongly binds with biotin and prevents its absorption. Thus, the ingestion of large quantities of raw egg white over a long period can result in a biotin deficiency. It has also been reported that antibiotics which damage the intestinal flora (thus decreasing bacterial synthesis) can reduce biotin levels. Interactions with certain anticonvulsant drugs and alcohol have also been reported, as they may inhibit intestinal carrier-mediated transport of biotin. Pantothenic acid ingested in large amounts competes with biotin for intestinal and cellular uptake because of their similar structures.

Deficiency

Human biotin deficiency is extremely rare. This is probably due to the fact that biotin is synthesised by beneficial bacteria in the human intestinal tract. Potential deficiency symptoms include anorexia, nausea, vomiting, glossitis, depression, dry scaly dermatitis, conjunctivitis and ataxia, and after long-lasting, severe biotin deficiency, loss of hair colour and hair loss (alopecia). Signs of biotin deficiency in humans have been demonstrated in volunteers consuming a biotin-deficient diet together with large amounts of raw egg white. After 3-4 weeks they developed a fine dry scaly desquamating dermatitis, frequently around the eyes, nose, and mouth. After ten weeks on the diet, they were fatigued, depressed and sleepy, with nausea and loss of appetite. Muscular pains, hyperesthesia and paresthesia occurred, without reflex changes or other objective signs of neuropathy. Volunteers also developed anaemia and hypercholesterolaemia. Liver biopsies in sudden infant death syndrome babies reveal low biotin levels. Most of the affected infants were bottle-fed.

Disease prevention and therapeutic use

There is no direct evidence that marginal biotin deficiency causes birth defects in humans, but an adequate biotin intake/supplementation during pregnancy is advisable.

Biotin is used clinically to treat the biotin-responsive inborn errors of metabolism, holocarboxylase synthetase deficiency and biotinidase deficiency.

Large doses of biotin may be given to babies with a condition called infantile seborrhea or to patients with genetic abnormalities in biotin metabolism. A large number of reports have shown a beneficial effect of biotin in infant seborrheic dermatitis and Leiner's disease (a generalised form of seborrheic dermatitis).

Biotin supplements are sometimes given to help reduce blood sugar in diabetes patients. People with type 2 diabetes often have low levels of biotin. Some patients with diabetes may have an abnormality in the biotin-dependent enzyme pyruvate carboxylase, which can lead to dysfunction of the nervous system.

The main benefit of biotin as a

dietary supplement is in strengthening hair and nails. Biotin supplements may improve thin or splitting toenails or fingernails and improve hair health. Uncomable hair syndrome in children also improves with biotin supplementation, as do certain skin disorders, such as “cradle cap”. Biotin has also been used to combat premature graying of hair, though it is likely to be useful only for those with a low biotin status. In orthomolecular medicine biotin is used to treat hair loss, but scientific evidence is not conclusive.

Biotin has been used for people in weight loss programs to help them metabolise fat more efficiently.

Recommended Dietary Allowance (RDA)

In 1998 the Food and Nutrition Board of the Institute of Medicine felt the existing scientific evidence was insufficient to calculate an EAR,

and thus an RDA, for biotin. Instead an Adequate Intake level (AI) has been defined. The AI for biotin assumes that current average intakes of biotin (35 µg to 60 µg/day) are meeting the dietary requirement. An estimation of the safe and adequate daily dietary intake for biotin was made for the first time in 1980 by the Food and Nutrition Board of the United States National Research Council. The present recommendations in the USA are 20-30 µg daily for adults and children over 11 years, and 5-12 µg daily for infants and younger children. France and South Africa recommend a daily intake of up to 300 µg, and Singapore up to 400 µg biotin. Others, including the Federal Republic of Germany, assume that diet and intestinal synthesis provide sufficient amounts.

Safety

No known toxicity has been associated with biotin. Biotin has been administered in doses as high as 40

mg per day without objectionable effects. Due to the lack of reports of adverse effects, no major regulatory authorities have established a tolerable upper level of intake (UL) for biotin.

Supplements and food fortification

Biotin, usually either in the form of crystalline D-biotin or brewer's yeast, is added to many dietary supplements, infant milk formulas and baby foods, as well as various dietetic products. As a supplement, biotin is often included in combinations of the B vitamins. Mono-preparations of biotin are available in some countries as oral and parenteral formulations.

Therapeutic doses of biotin for patients with a biotin deficiency range between 5 and 20 mg daily. Seborrheic dermatitis and Leiner's disease in infants respond to daily doses of 5 mg. Patients with biotinidase deficiency require life-long

Current recommendations in the USA

RDA*

Infants	< 6 months	5 µg (Adequate Intake, AI)
Infants	7-12 months	6 µg (AI)
Children	1-3 years	8 µg (AI)
Children	4-8 years	12 µg (AI)
Children	9-13 years	20 µg (AI)
Children	14-18 years	25 µg (AI)
Adults	> 19 years	30 µg (AI)
Pregnancy		30 µg (AI)
Lactation		35 µg (AI)

*The Dietary Reference Intakes (DRIs) are actually a set of four reference values: Estimated Average Requirements (EAR), Recommended Dietary Allowances (RDA), Adequate Intakes (AI), and Tolerable Upper Intake Levels, (UL) that have replaced the 1989 Recommended Dietary

Allowances (RDAs). The RDA was established as a nutritional norm for planning and assessing dietary intake, and represents intake levels of essential nutrients considered to meet adequately the known needs of practically all healthy people



biotin therapy in milligram doses (5-10mg/day). Patients with HCS deficiency require supplementation of 40-100 mg/day. If biotin therapy is introduced in infancy, the prognosis for both these genetic defects are good.

A daily supplement of 60 µg biotin for adults and 20 µg for children has been recommended to maintain normal plasma levels in patients on total parenteral nutrition.

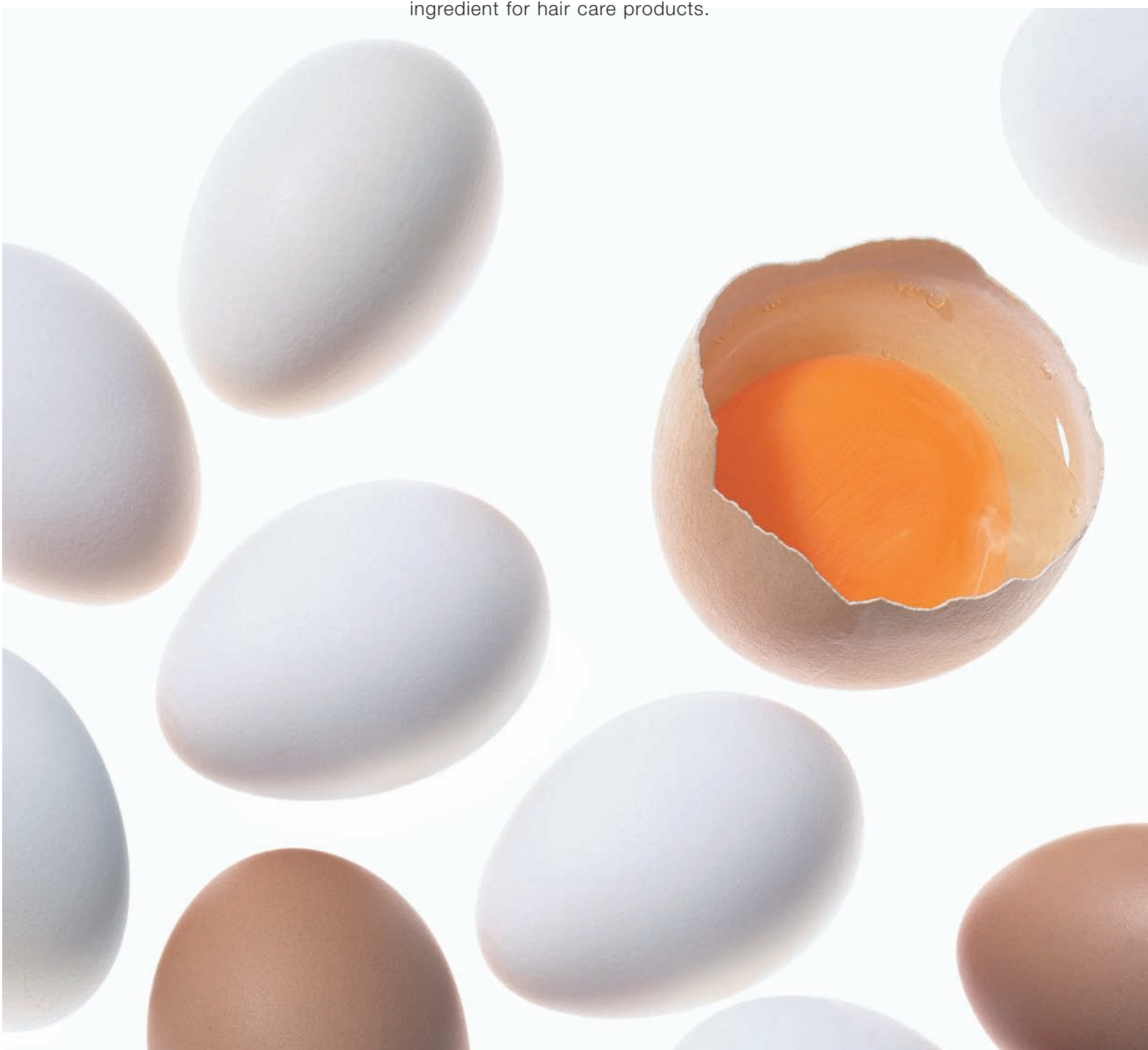
Other technical applications

Baker's yeast (*Saccharomyces cerevisiae*) is dependent on biotin for growth. Biotin is therefore added as a growth stimulant to the nutrient medium used in yeast fermentation. Also, many of the microorganisms used in modern biotechnology are biotin-dependent. Thus, biotin is added to the growth medium in such cases.

In cosmetics, biotin is used as an ingredient for hair care products.

Industrial production

Commercial synthesis of biotin is based on a method developed by Goldberg and Sternbach in 1949 and using fumaric acid as starting material. This technique produces a pure D-biotin which is identical to the natural product.



History

- 1901** Wildiers discovers that yeast requires a special growth factor which he names “bios”. Over the next 30 years, bios proves to be a mixture of essential factors, one of which – bios IIB – is biotin.
- 1916** Bateman observes the detrimental effect of feeding high doses of raw egg white to animals.
- 1927** Boas confirms the findings of dermatosis and hair loss in rats fed with raw egg white. She shows that this egg white injury can be cured by a “protective factor X” found in the liver.
- 1931** György also discovers this factor in the liver and calls it vitamin H (from Haut, the German word for skin).
- 1933** Allison and coworkers isolate a respiratory coenzyme – coenzyme R – that is essential for the growth of *Rhizobium*, a nitrogen-fixing bacterium found in leguminous plants.
- 1935** Kögl and Tönnis extract a crystalline growth factor from dried egg yolk and suggest the name ‘biotin’.
- 1940** György and his associates conclude that biotin, vitamin H and coenzyme R are identical. They also succeed in isolating biotin from the liver.
- 1942** Kögl and his group in Europe and du Vigneaud and his associates in the USA establish the structure of biotin.
- 1942** Sydenstricker and colleagues demonstrate the need for biotin in the human diet.
- 1943** Total synthesis of biotin by Harris and colleagues in the USA.
- 1949** Goldberg and Sternbach develop a technique for the industrial production of biotin.
- 1956** Traub confirms the structure of biotin by X-ray analysis.
- 1959** Lynen's group describes the biological function of biotin and paves the way for further studies on the carboxylase enzymes.
- 1971** First description of an inborn error of biotin-dependent carboxylase metabolism by Gompertz and associates.
- 1981** Burri and her colleagues show that the early infantile form of multiple carboxylase deficiency is due to a mutation affecting holocarboxylase synthetase activity.
- 1983** Wolf and coworkers suggest that late-onset multiple carboxylase deficiency results from a deficiency in biotinidase activity.



Paul György



Fritz Kögl



Vincent du Vigneaud



Feodor Lynen