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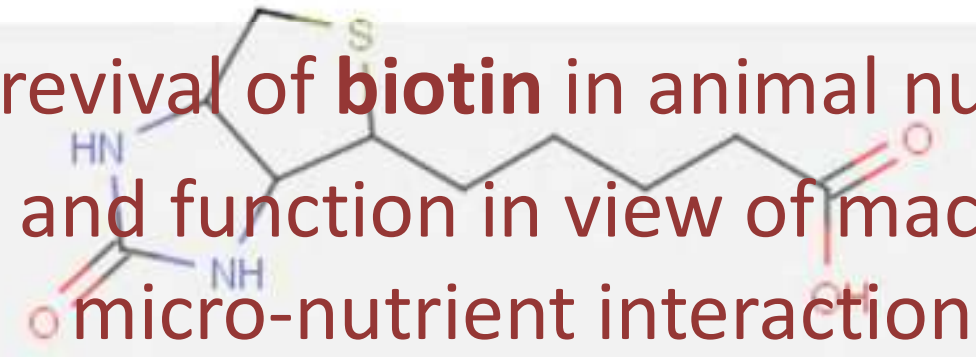
The revival of **biotin** in animal nutrition. Role and function in view of macro- and micro-nutrient interactions



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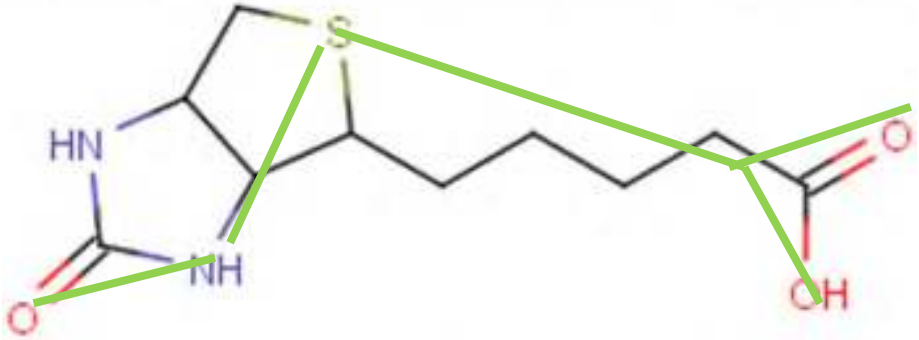
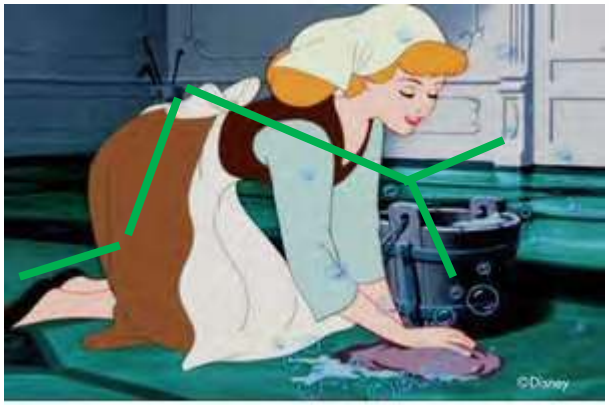
Premise

For several decades very little research was published on the effects of biotin



Biotin can be considered as a Cinderella within vitamin B group



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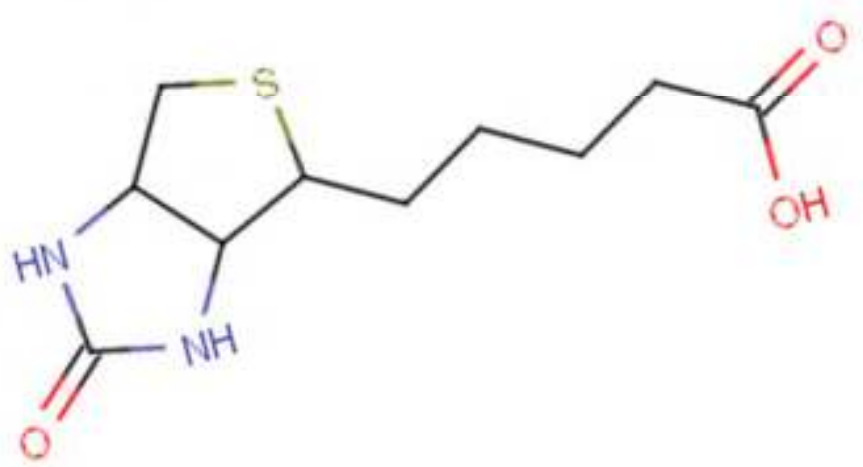
Premise

Was it because easily available in food?

Or because synthesized by gut microflora?

Or was it for AVIDIN?



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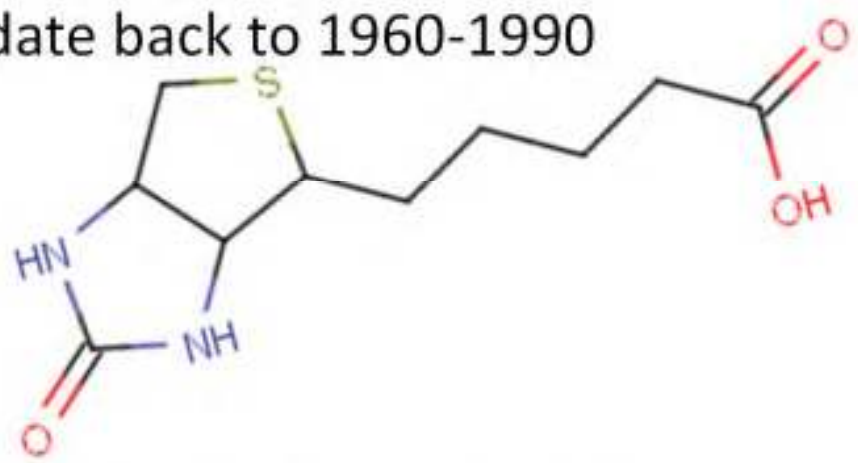
History (just a bit)

The large part of biotin researches date back to 1960-1990



Only some investigations were carried out in the 21st century

We are now assisting to a revival of biotin role and functions

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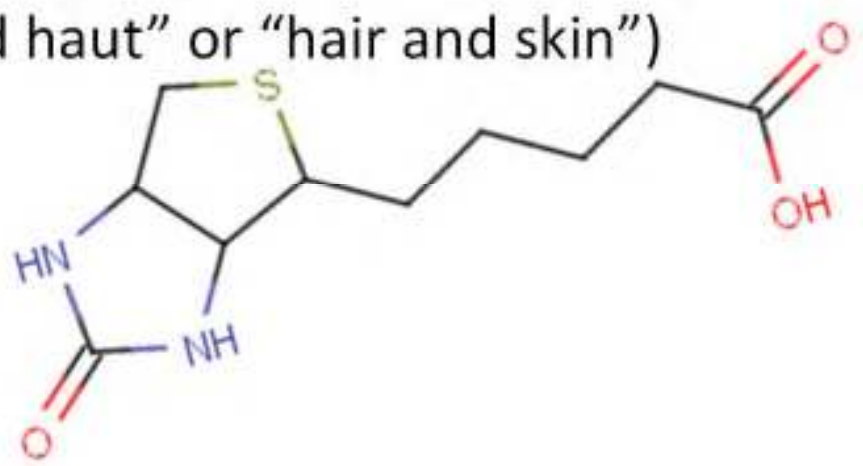
History (just a bit)

Also known as Vitamin H (“haar und haut” or “hair and skin”)

IUPAC nomenclature is biotin!



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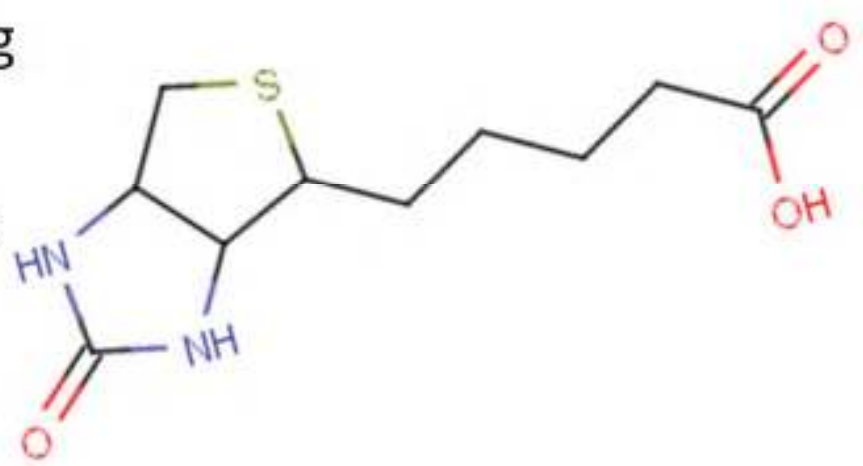
History (just a bit)

The chemical structure is interesting

Biotin is a monocarboxylic acid with a side chain (bond to Lysin)



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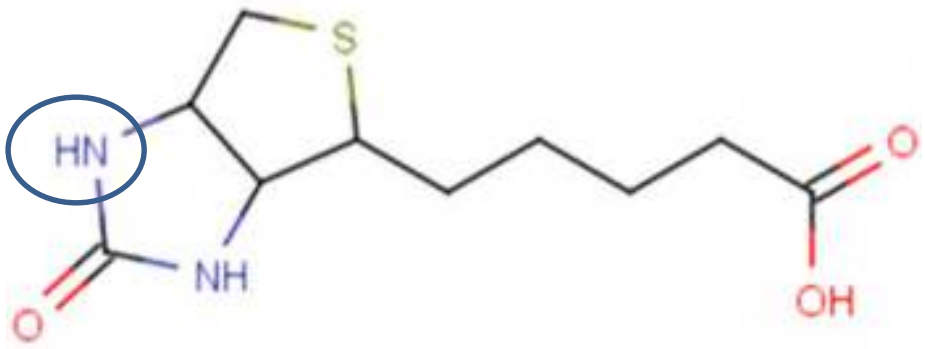
History (just a bit)

The nitrogen atom opposite the side chain acts as a transfer point for carboxyl groups in enzymatic carboxylation reactions, which is the primary function of biotin enzymes **(Bonjour, 1991)**.



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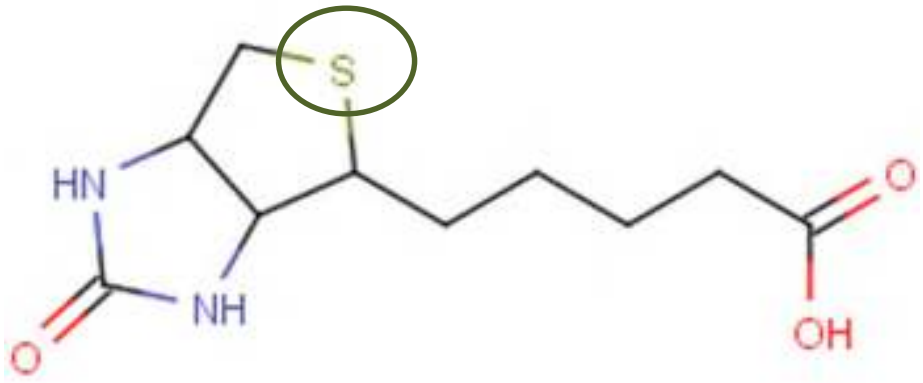
History (just a bit)

The sulfur atom is present as a thioether bond. Oxidation of the sulfur atom forms either biotin sulfoxide or biotin sulfone, which are metabolically inactive.



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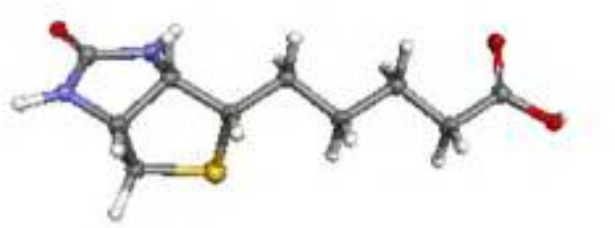
History (just a bit)

Biotin contains three asymmetric (chiral) carbon atoms; therefore, eight different isomers are possible. Of these isomers, only D-biotin is found in nature and is biologically active (**Mock, 1990**)



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Sources of biotin

Biotin is present in feedstuffs in both **bound** and **free** forms, and much of the bound biotin is apparently unavailable to animal species. For poultry and swine (and presumably for ruminants), often less than half of the microbiologically determined biotin in a feedstuff is biologically available (**Scott, 1981; Frigg, 1984, 1987; Saueret al., 1988**)

Table- Biotin content in some feedstuffs

Feed	biotin, mg/kg DM
Starchy grains	0.090
Soybean meal	0.270
Wheat midds	0.330
Hay crop forages	0.450
Distillers/brewers grains	0.600
Cane molasses	0.800

Sources of biotin

Naturally occurring biotin is often bound to the amino acid *lysine*, in a form called **biocytin**.

Biotinidase is a mammalian enzyme that cleaves the biotin-lysine amide bond, freeing biotin for reuse in metabolism.

Biotinidase is present in pancreatic secretions and intestinal cells of mammals, as well as systemically.

The brush border of the enterocyte is a site of cleavage

Sources of biotin

Experimental feeding trials in different animals species have shown that biotin is absorbed intact in the first third to half of the small intestine by both active transport and diffusion (**Bonjour, 1991; Zempleni and Mock, 1999**).

In addition, biotin is absorbed from the hind-gut of the pig.

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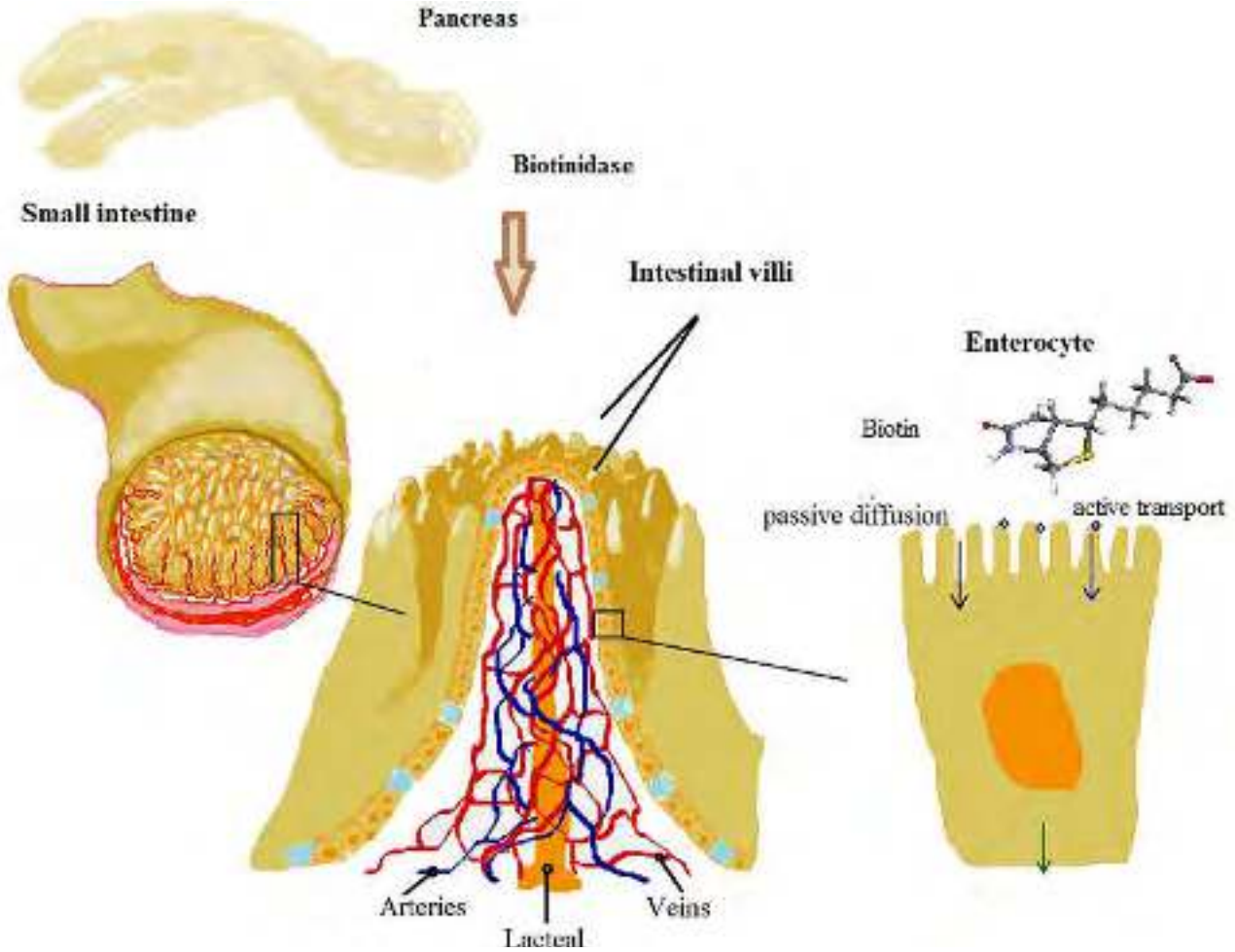
Fate of biotin



Sources of biotin

Naturally occurring biotin is found partly in the free state (fruit, milk, vegetables) and partly in a form bound to protein in animal tissues, plant seeds and yeasts.

! If genetically encoded biotinidase deficiency occurs, then bound biotin in the form of biocytine is compromised, independently on dietary intake.

! If gut microflora is disturbed, also biotin availability for the host decreases.

! If enteral problems occur, also cleavage and absorption of biotin are affected

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Summing up

Biotin was largely studied in the beginning of the 20th century

Most of advanced knowledge belongs to 1960-1990

Despite this, its tertiary structure is of absolute Importance to explain the biological role.

As water soluble, it is easily excreted with urine

Severe deficiency of biotin is rare, unless experimentally induced.

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Experimental biotin deficiency in poultry (1969)

Note lesion at apex of mouth in biotin-deficient poult.

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Experimental biotin deficiency in pigs

The two pigs in the middle are biotin deficient. Note the hair loss and dermatitis.

Courtesy of T.J. Cunha and Washington State University

Note transverse cracking of the soles and the tops of the hooves of biotin-deficient pigs.

Courtesy of T.J. Cunha and Washington State University

Experimental biotin deficiency: clinical sings

In experiments carried out on volunteers in 1916, 1927, 1931 fed with avidin in the diet (one avidin mole binds 4 biotin moles), biotin deficiency led to clinical conditions including scaly dermatitis, spectacle reddish eye, fatigue, poor nail and hair quality.

In animals it is teratogenic.

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Biotin deficiency

Since biotin deficiency in common practice was rare (or never reported) the interest about this vitamin was low.

Diagnostic limit…

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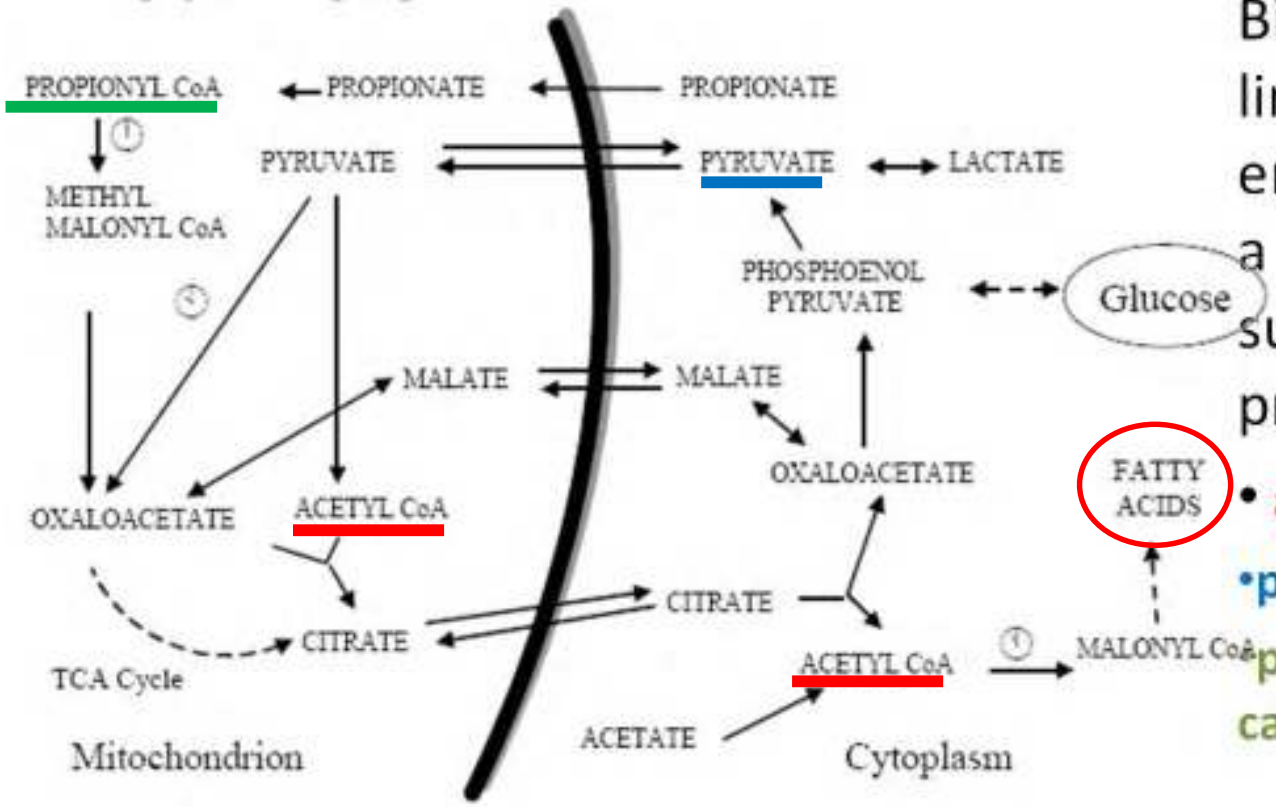
Biotin role



Biotin is covalently linked to each of these enzymes and transfers a carbon unit from the substrate to the product:

- acetyl-CoA carboxylase
- pyruvate carboxylase
- propionyl-CoA carboxylase

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Biotin role at sub-cellular level

Biotin is an essential coenzyme in carbohydrate, fat and protein metabolism!!!

- normal blood glucose levels via the gluconeogenic enzymes
- fatty acids biosynthesis
- tricarboxylic acid cycle
- anaplerosis and pleiotropic gene regulation, for genes of carbohydrate metabolism

Biotin is also a cofactor in **beta-methylcrotonyl-CoA-carboxylase**, which catalyzes an essential step in leucine catabolism.

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Biotin role at tissue level

•Biotin is an essential nutrient in keratin synthesis and lipogenesis, the two major metabolic pathways in **keratinization**.

• Biotin is required for normal synthesis of long-chain unsaturated fatty acids and essential fatty acid metabolism. Deficiency in rats and chicks inhibited arachidonic acid (20:4) synthesis from linoleic acid (18:2) while increasing linolenic acid (18:3) and its metabolite (22:6) **(Kramer et al., 1984; Watkins and Kratzer, 1987a).**

• Biotin is also required for normal function of immune cells that actively accumulate biotin. Populations of T- and B-lymphocytes are dependent on biotin supply **(Bonjour, 1991; Zempleni and Mock, 1999).**

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Biotin role at tissue level

- Especially those tissue with high rates of metabolic activity or cell division are susceptible of disorders from marginal biotin deficiency

(Hoof horn, hairs, skin); (high producing tissues, pregnancy-lactation-growth); (Immune system); (heart muscle and nervous system)….

Therefore, biotin homeostasis is crucial for maintaining

normal body functions

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Biotin role at tissue level

In dairy cattle, supplementation, although milk production was not improved, demonstrated improved metabolic status.

- blood glucose concentrations were higher
- blood nonesterified fatty acid (NEFA) concentrations were lower
- lower NEFA concentrations indicate that the cows supplemented with biotin were mobilizing less body fat to support their milk production.

Biotin supplementation also decreased liver fat in postpartum Biotin has previously been shown to reduce the incidence of fatty liver and kidney syndrome in rapidly growing broiler chickens (McDowell, 2000).

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The revival of Biotin

• Independent research groups very very recently (2016-2019) have started to focus on biotin and its homeostasis.

•Most of results are oriented to recommendations for humans

•Most of investigations are carried out on lab animals (mice, rats)

• But they started looking at old animal studies

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KEY FACTS

- Establishing biotin status in individuals is extremely difficult

- Circulating values change hugely and are difficult to related to dietary intake only

- Marginal biotin deficiency is often subclinical (no pathognomic signs??? But rather non-specific overall status involvement???)

- Biotin deficiency can be estimated by side-products of biotin metabolism Lymphocyte PCC (propionyl Co-Carboxylasa) and urinary HIA (hydroxyisovaleric acid).

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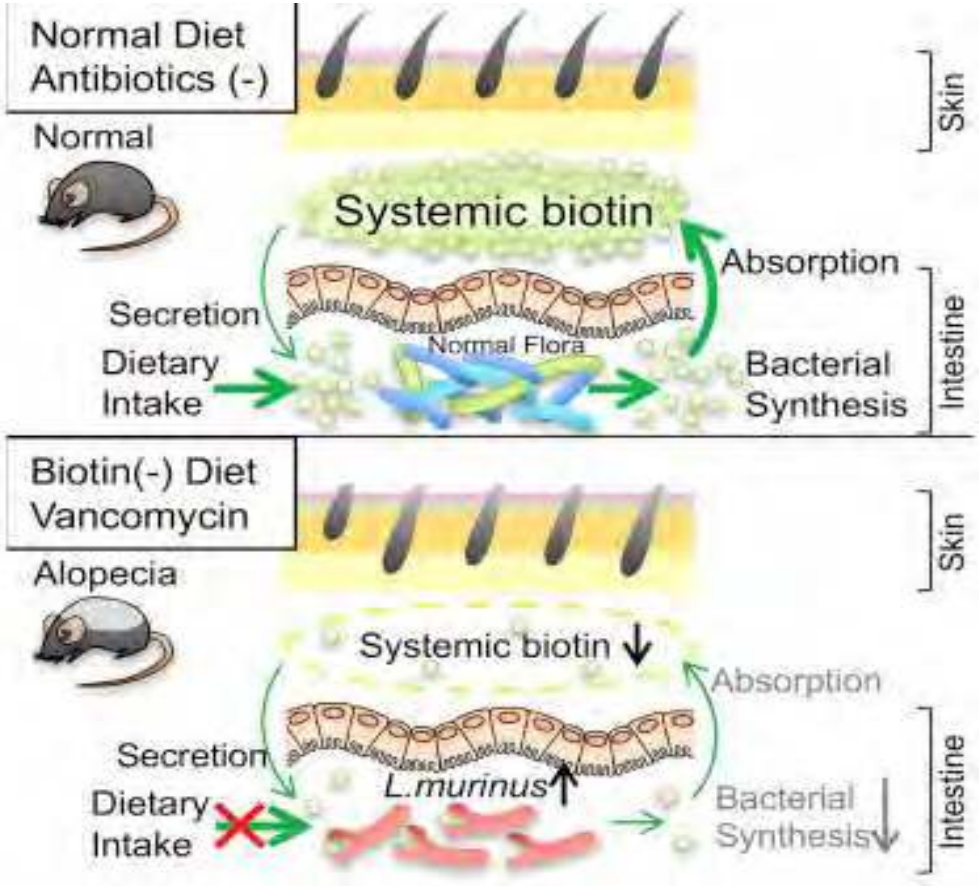
The revival of Biotin



- Hayashi et al., 2017

Gut microbiota metabolism affects host physiology beyond the gastrointestinal tract. Here, antibiotic-induced gut dysbiosis leads to the development of alopecia in mice on a biotin-deficient diet

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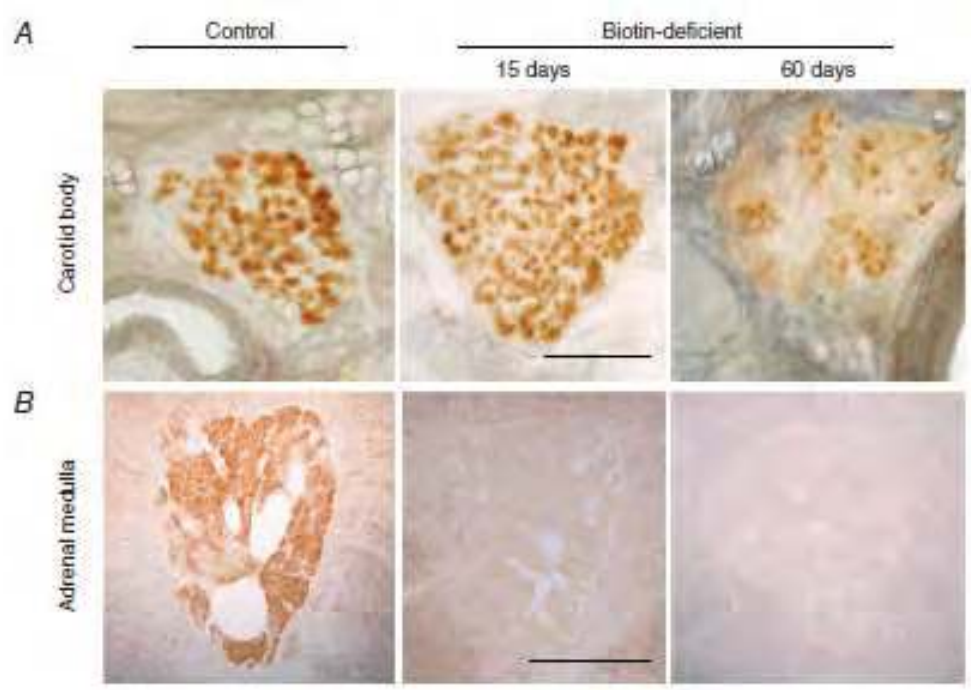
The revival of Biotin



Ortega et al., 2016

In biotin-deficient rats biotin rapidly disappears from the blood; however, it remains at relatively high levels in CB glomus cells.

The CB contains high levels of mRNA for SLC5a6, a biotin transporter

dopamine transport and/or storage in small secretory granules in glomus cells depend on biotin

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Conclusion

Studies with poultry and swine indicate that those species can safely tolerate dietary levels four to 10 times their nutritional requirements of biotin (NRC, 1987)

In view of the rapid metabolic turnover of biotin, toxicity is unlikely to occur in livestock

However, it has been recently reported that reproduction function was compromised by excess of biotin intake, leading to sterile female rats.

So, CAUTION!

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Conclusion

Thank you!