Clinical symptoms of biotin deficiency in animals[1]

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The main biochemical function of biotin, one of the B complex group of vitamins, is as a coenzyme in certain enzymatic reactions associated with decarboxylation and carbon dioxide fixation. It thus has an important role in intermediary metabolism (1).

Biotin is so widely distributed in foods and so abundantly produced by intestinal bacteria that it is doubtful whether a spontaneous biotin deficiency ever occurs in the adult animal unless a biotin antagonist is present in the diet. The only antagonist likely to be of importance in human nutrition is avidin, a protein constituent of egg white. Avidin, if present in the diet, combines with biotin in the alimentary tract, thus rendering the vitamin unavailable. The avidin may be denatured and inactivated by prolonged heating of the egg white, although spray drying or heating at 40 C for 3 hr does not completely destroy its biotin-binding properties. The normal method of producing a biotin deficiency in human and animal studies is by feeding raw egg white. However, care should be exercised in interpreting such experiments, because reports have indicated that diets containing high levels of raw egg white or lower levels in combination with rancid oils can produce toxic effects which although similar to are not those of a biotin deficiency (2, 3).

In humans, possibly the only symptom of a spontaneous biotin deficiency is the seborrheic dermatitis sometimes observed in very young infants (4, 5). This deficiency of biotin is assumed to arise because of the low biotin content of human breast milk and/or failure to absorb the vitamin because of defective digestion or persistent diarrhea (5, 6). Bhagavan (7) has observed that the blood biotin content of women decreases during pregnancy and is significantly lower than that in normal adults, and Nisenson (5) has reported that seborrheic dermatitis in breast-fed infants may be cured by giving biotin to the nursing mothers. However, the connection between biotin and seborrheic dermatitis is still questioned (8).

The clinical symptoms of adult human egg white biotin deficiency have been described by Sydenstricker et al. (10). In this study the deficiency was experimentally induced by feeding dessicated egg white. The symptoms observed included dermatitis, glossitis, anorexia, nausea, sitophobia, mental depression, pallor, muscle pain, hyperesthesia, paresthesia, anemia, hypercholesterolemia, and electrocardiographic abnormalities. Most of these symptoms were also found in a more recent case of egg white injury (11). However, in contrast to the earlier report, these latter workers were unable to show any anemia, hypercholesterolemia, muscle pain, or electrocardiographic abnormality. However, investigations with nonhuman subjects have indicated characteristic gross fatty change in heart muscle and degeneration of purkinje cells in biotin-deficient ducks (12) and metabolic changes in rat heart muscle as reflected by abnormal electrocardiograms (13). Petrelli et al. (14) have also observed an increased number of circulating erythrocytes and a reduced hemoglobin value in biotin-deficient rats and

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hypercholesterolemia has also been observed in biotin-deficient humans (15) and rats (16, 17) but not chicks (18). Alopecia is a characteristic finding in animal studies (19, 20), and similar findings have been observed in humans (15).

Investigations into the effects of biotin deficiency have been confined to a few species, notably the rat and chick, and little attention has been paid to the derangement of metabolism in human biotin deficiency. This is probably due to the fact that under normal conditions few confirmed spontaneous clinical biotin deficiencies have been reported in humans. Nevertheless, the fact that so few studies have been reported concerning biotin avitaminosis in humans suggests that animal studies may reveal other symptoms of biotin deficiency which might also be found in biotin-deficient humans. Although certain effects of biotin deficiency, such as embryonic development in the rat and chick (9), vary between animal species, there are considerable similarities in many known clinical symptoms between humans and other species (see above).

Biotin is a cofactor for the lipogenic enzyme acetyl CoA carboxylase, and a deficiency of this vitamin reduces fatty acid synthesis through a reduction in the activity of this enzyme. Although in many instances the lipid contents of liver and carcass have been reduced in biotin deficiency, there have been a number of reports indicating a fatty liver development (20–22). The exact conditions under which fatty infiltration of the liver occurs have not yet been defined. However, a fatty liver condition observed with rapidly growing poultry, called the fatty liver and kidney syndrome, has been shown to be responsive to biotin therapy (23, 24). This syndrome is produced by stress combined with low dietary biotin levels. These factors result in low liver biotin concentrations (25) and increases in the specific activities of hepatic lipogenic enzymes (25, 66). The importance of stress in the development of fatty liver and kidney syndrome in chicks has also been reported by Whitehead et al. (26). One of the symptoms of avian fatty liver and kidney syndrome is a rapid and sometimes high mortality, and Johnson et al. (25) have suggested that a biotin deficiency combined with stress may be involved in the sudden and inexplicable deaths that occur in many species of animals. The evidence indicates that death occurs as a result of an insufficiency of biotin for pyruvate carboxylase, so that under stress conditions insufficient glucose is synthesised by gluconeogenesis (25, 64–66).

Fatty acid composition is considerably altered in biotin deficiency. The major changes relate to increases in the relative proportions of the 16-carbon fatty acids, especially palmitoleic acid (21, 22, 27–31). The relative increase in liver palmitoleic acid may be suitable for diagnostic use.

Some reports indicate that cholesterol synthesis is increased in biotin deficiency at a time when fatty acid synthesis is reduced (18, 32). Although liver cholesterol levels are generally unaffected (16, 18, 21, 22), the serum (15–17) and carcass (18, 21) cholesterol levels are increased. Some reports have indicated that biotin treatment accelerates the removal of lipids from the walls of the aorta and coronary arteries and prevents atherosclerosis in rabbits fed cholesterol (33, 34), although Pool et al. (35) have reported that biotin does not reduce serum cholesterol or the degree of aortic atheroma in rabbits given an atherogenic diet containing either cholesterol or beef tallow. Balnave (36) has observed reduced hepatic lipogenic enzyme activity and liver lipid content in poultry given excessive amounts of biotin.

Experimental work has indicated that there are many similarities in carbohydrate metabolism between diabetic and biotin-deficient rats, and the responses of the diabetic and the biotin-deficient rat to biotin or insulin treatment are remarkably similar. For example, insulin increases liver glucokinase activity in the biotin-deficient rat (37), whereas biotin stimulates the activity of this enzyme and the other key glycolytic enzymes, phosphofructokinase and pyruvate kinase, in the alloxan diabetic rat (38). Similarly, insulin restores the activity of liver hexokinase in biotin-deficient chicks (39). The glucose tolerance curve and urinary ketone body excretion in the biotin-deficient rat indicate certain similarities to diabetes, and injection of insulin brings about an im-

provement in the synthesis of liver glycogen from glucose and the incorporation of leucine into liver microsomal protein (40). In diabetic animals cholesterol synthesis in enhanced, fatty acid synthesis is decreased, and the development of ketosis is increased in a fashion similar to that in biotin-deficient animals. However, biotin deficiency has apparently no effect on insulin levels (41) or on the histology of the β-cells of the islets of Langerhans (40). Oxman and Ball (42) have shown that insulin enhances the uptake of glucose in vitro by adipose tissue from both normal and biotin-deficient rats, although much more glucose is metabolized to lactic acid in deficient tissues.

Okey et al. (19) have indicated that sex hormones alter the need for, and the capacity of the animal to respond to, biotin, so that there are sex differences in the rate of development and degree of deficiency observed in biotin avitaminosis. Biotin deficiency was induced much more easily in male than in female rats, and testosterone implants in both sexes increased the severity of a mild biotin deficiency. In addition, gonadectomy produced only slight changes in deficiency symptoms in biotin-deficient male rats but in females it produced a marked increase in the incidence and severity of biotin deficiency symptoms. However, reports (43, 44) have indicated that gonadal hormones have little effect on the patterns of reponse to biotin deficiency of avian hepatic and oviducal enzyme-specific activities.

Biotin deficiency severely retards all facets of reproductive function in rats and chicks (9). In addition, certain reproductive disorders in male and female rats, produced as a result of biotin deficiency, fail to respond to biotin even though the external clinical symptoms of the deficiency have disappeared. For example, Delost and Terroine (45) observed that in the biotin-deficient male rat the lesions of the reproductive system responded to testosterone or gonadotrophin, whereas biotin, although relieving the external signs of deficiency, induced only slight improvements in the sexual organs. Okey et al. (19) also observed that in female rats the ovarian atresia observed in biotin deficiency failed to respond to biotin treatment although all external symptoms of biotin deficiency had disappeared. Communal (46) reported that histological lesions of the testis persist even when male rats are clinically cured of a biotin deficiency, and Rose et al. (47), studying successive filial generations of rats fed normal diets, even suggested that abnormalities of reproduction are inherited by descendants of biotin-deficient parents. Whether or not this latter suggestion is correct it is apparent that although the external symptoms of biotin deficiency may rapidly disappear in response to biotin therapy, certain reproductive lesions may not be cured by vitamin administration alone.

As well as the important relationship noted above between the biotin status and sex hormone status of an animal, certain interrelationships exist between biotin and other vitamins which may have significant effects on both the metabolism and vitamin requirements of animals (9, 48–50). Much of this work relates to the interrelationships between biotin, ascorbic acid, vitamin B_{12}, and folic acid. The rate of synthesis of biotin in the intestinal tract is dependant on dietary composition (51, 52), and certain antibiotics and sulfa drugs can accentuate or induce biotin deficiency symptoms by altering the nature of the intestinal flora (52, 53). These factors may have an important influence on the biotin requirements of animals.

In the chick, biotin is necessary for normal maturation of bone, although cell proliferation and integrity are not affected (54). The many references to hock joint disorders in chicks and turkeys may be an indication that biotin is required for normal bone development (50, 55, 56).

Subclinical manifestations of biotin deficiency are also evident in that antibody production is impaired (57–59) and there is a reduced resistance to certain diseases (60, 61). Wound healing is also retarded in biotin-deficient rats (19, 62). Furthermore, exposure to cold has resulted in the death of biotin-deficient rats, although no signs of adrenal insufficiency were observed (63). This is a further indication (25) that the biotin-deficient animal has a reduced ability to resist stress.

Summary

Under normal conditions, few confirmed spontaneous clinical biotin deficiencies have been reported in humans. However, a deficiency may be induced if a biotin antagonist such as avidin, a protein constituent of raw egg white, is fed.

Only a few reports relating to biotin deficiency concern human subjects. However, there are considerable similarities in many known clinical symptoms between humans and other species. It is apparent from animal studies that biotin is involved in a wide range of metabolic disturbances.

Apart from the known clinical symptoms of human egg white injury biotin deficiency may result in major changes in lipid metabolism. These include fatty liver development, increased liver palmitoleic acid content, and increased serum and carcass cholesterol levels. A biotin deficiency combined with stress causes a rapid and sometimes high mortality in young chickens.

There are many similarities in carbohydrate metabolism between diabetic and biotin-deficient rats, and the responses of the diabetic and the biotin-deficient rat to biotin and insulin are remarkably similar.

Sex differences occur in the rate of development and degree of deficiency observed in biotin avitaminosis. Although biotin deficiency retards all facets of reproductive function in rats, certain reproductive disorders fail to respond to biotin even though the external clinical symptoms of the deficiency have disappeared.

Important interrelationships exist between biotin and other vitamins, which may affect the metabolism and vitamin requirements of animals. Dietary composition as well as certain antibiotics and drugs can influence the intestinal synthesis of biotin and hence the biotin requirements of animals.

Biotin deficiency may also prevent normal maturation of bone, impair antibody production and wound healing, and reduce resistance to certain diseases.

The importance of biotin in human nutrition merits further investigation. Areas of special interest include *1*) the nutrition of the young infant, *2*) the possible connection between stress and sudden and unexpected deaths in biotin deficiency, *3*) the psysiological significance of biotin in lipid metabolism and in the treatment of atherosclerosis, and *4*) the relationship of biotin to the production and action of hormones such as insulin and the sex hormones.

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