Biotin Disorders

14

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Contents

Summary
Disorders in the processing of biotin present with deficiencies of the biotin-dependent carboxylases, i.e., multiple carboxylase deficiency. The biochemical and clinical abnormalities reflect those observed in individual, isolated defects of three mitochondrial carboxylases: methylcrotonyl-CoA carboxylase, propionyl-CoA carboxylase, and pyruvate carboxylase. Multiple carboxylase deficiency is caused by defects in holocarboxylase synthetase or in biotinidase. Treatment of biotinidase deficiency with biotin supplementation is highly effective in reversing the abnormalities, and that is usually also the case for the treatment of holocarboxylase deficiency, though there may be some variability of response.

14.1 Introduction

Biotin is a vitamin cofactor used in carboxylation reactions which fix CO_2 from bicarbonate to substrates to generate carboxylic acid moieties; in fact each biotin-dependent reaction in human metabolism converts a carboxylic acid (or CoA ester) to a dicarboxylic acid (or CoA ester). In its active form, and the form most often ingested, biotin is covalently bound to lysine on the carboxylase holoenzyme. Utilization of biotin requires its transfer to the correct lysine residue of the carboxylase apoenzymes to generate the active holoenzymes, a reaction carried out by holocarboxylase synthetase (HCS). Recovery of biotin, from endogenous carboxylase proteins as they are proteolyzed and from most protein-bound dietary sources, requires cleavage of the lysine conjugate (biocytin), a reaction catalyzed by the enzyme biotinidase. Deficiency of biotinidase or HCS causes a functional defect in all the carboxylases, termed multiple carboxylase defect (MCD).

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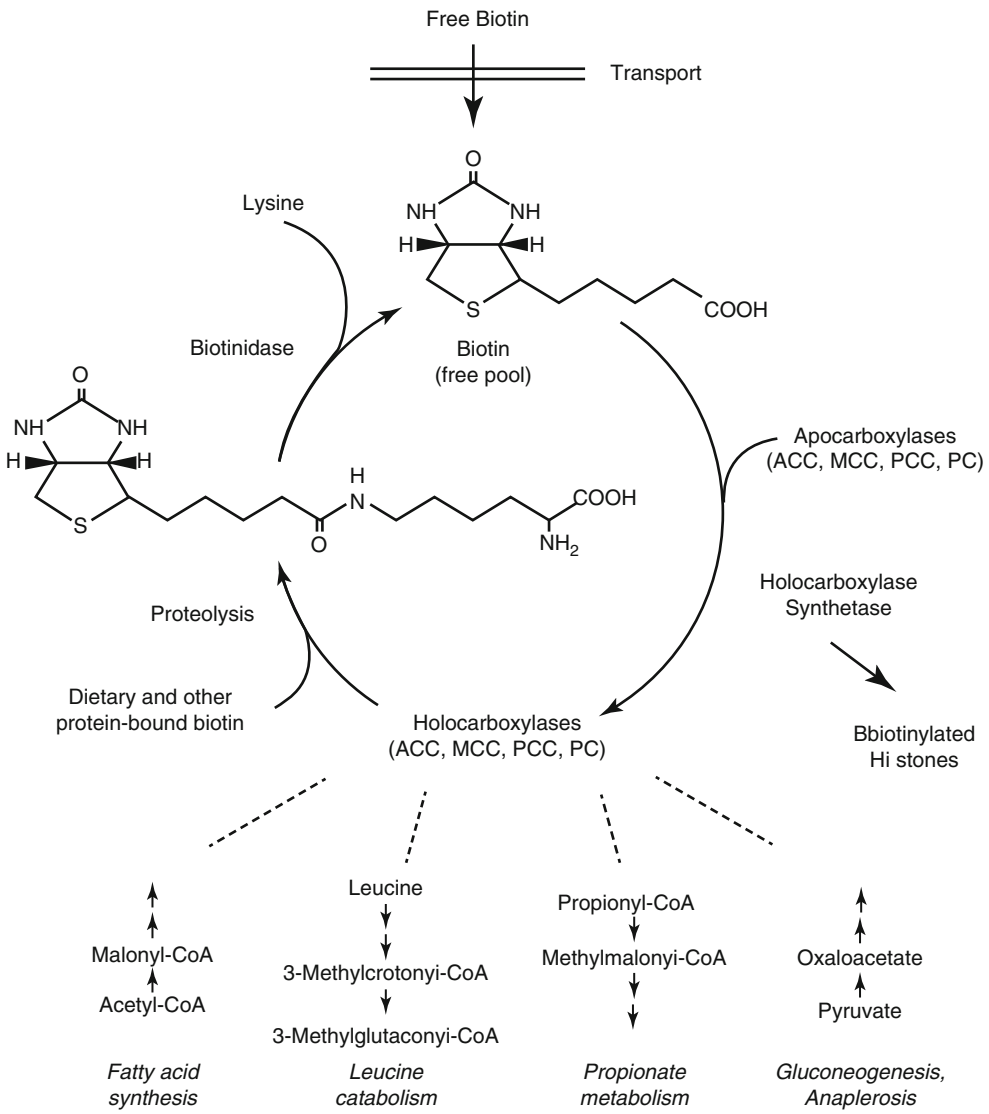
14.2 Nomenclature

No.	Disorder	Alternative Name	Abbreviation	Gene symbol	Chromosomal localization	Affected protein	OMIM no.	Subtype
14.1	Biotinidase deficiency	Late-onset multiple carboxylase deficiency	BTD deficiency	BTD	3p25.1	Biotinidase	253260	All forms
14.2	Holocarboxylase synthetase deficiency	Infantile-onset multiple carboxylase deficiency	HCSD	HLCS	21q22.13	Holocarboxylase synthetase	253270	All forms

14.3 Metabolic Pathways

Fig. 14.1



HCS is a complex enzyme which activates biotin to form D-biotinyl-5′-adenylate and then catalyzes the attachment of the biotin to an active site ε-amino group of a lysine residue of the newly synthesized apocarboxylase enzyme. The covalent binding to biotin conveys enzymatic activity and holocarboxylase status to the apocarboxylase protein.

There are four biotin-dependent enzymes in human metabolism. Acetyl-CoA carboxylase (ACC) is used to generate malonyl-CoA which is important in initiation of the synthesis of fatty acids and regulation of their oxidation. ACC is present in two isomers, one of which (ACC1) is cytoplasmic and the other of which (ACC2) is associated

with the endomembrane system (including primarily the cytosolic side of the outer mitochondrial membrane). There are as yet no know disorders due to defects in ACC, but the other three carboxylases, which are all localized to the mitochondrial matrix, each have a disease state associated with its deficiency. These include methylcrotonyl-CoA carboxylase (2 subunits, MCCC1 and MCCC2), propionyl-CoA carboxylase (2 subunits, PCCA and PCCB), and pyruvate carboxylase (PC).

The first patient ascertained with MCD had HCSD and was described in 1971 (Gompertz et al. 1971) as having an abnormality of leucine metabolism due to identification of 3-methylcrotonylglycine and 3-hydroxyisovaleric acid in the urine. A defect was found in 3-methylcrotonyl-CoA carboxylase (Gompertz et al. 1973). When methylcitric and hydroxypropionic acids were also found to be increased in the same patient in 1977 (Sweetman et al. 1977), enzymatic analysis revealed defective activity of propionyl-CoA carboxylase (Weyler et al. 1977) in addition. The third mitochondrial carboxylase, pyruvate carboxylase, was also shown to be defective in activity (Saunders et al. 1979), and the disorder was then renamed multiple carboxylase deficiency.

14.4 Signs and Symptoms

Holocarboxylase Synthetase Deficiency. Patients with HCS deficiency generally present in the first days or months of life with overwhelming illness identical to those of propionic acidemia or other classic organic acidemia. The age of onset of clinical symptoms generally has generally been before 6 weeks of life (Burri et al. 1985), but it is clear that patients with an abnormal holocarboxylase synthetase can present at any age from 1 day to 6 years of age (Suormala et al. 1997; Sherwood et al. 1982).

In the acute episode of illness, the infant has massive ketosis and metabolic acidosis with an anion gap. There may be tachypnea or Kussmaul breathing, and blood ammonia may be elevated. The episode may progress to dehydration and deep coma, and a number of patients have died of this disease; the initial episode may be lethal within hours of birth (Sweetman et al. 1982). Cutaneous features are an integral part of the untreated disease, though some patients have died before the development of skin lesions, and now patients are being treated before the development of cutaneous lesions. An erythematous eruption may involve the entire body, with bright red, scaly, or desquamative lesions. Complicating monilial infection is common. Varying degrees of alopecia are seen, including alopecia totalis, with absence of eyelashes, eyebrows and lanugo, as well as the hair of the head. There may be persistent vomiting and failure to thrive. Neurological abnormalities appear to be related to the effects of the initial or subsequent episodes of illness, which might include decreased brain perfusion and hyperammonemia; with treatment and while compensated, the neurological function is otherwise expected to be normal, and the neurological examination may be normal despite a hyperammonemic episode (Dabbagh et al. 1994). Muscular hypotonia and hypertonia have been described, as have more severe forms of dystonia and movement disorders, including athetosis and opisthotonus. There may be electroencephalographic abnormalities and abnormal findings on cranial computed tomography or magnetic resonance imaging, particularly involving the white matter. Subependymal cysts were observed in one infant and reported to disappear following 6 months of treatment (Squires et al. 1997), and subependymal cysts were also observed in 7 Samoan infants who had severe disease, incomplete responsiveness to biotin, and early life-threatening metabolic events (Wilson et al. 2005), as well as a Samoan infant in an earlier series, who had a poor dermatological response to biotin (Sweetman et al. 1982).

The biochemical hallmark of this disease is the excretion of 3-hydroxyisovaleric acid and 3-methylcrotonylglycine, plus elevated quantities of lactic acid in blood and urine. The first clinical chemical clue to the disease may be the discovery of lactic acidemia. Organic acid analysis during an acute acidosis also reveals methylcitric and 3-hydroxypropionic acids and may also include tiglylglycine (Sweetman et al. 1982). The excretion of 3-hydroxyisovaleric acid is almost always greater than that of 3-methylcrotonylglycine and may be as high as 200 times normal (Sweetman et al. 1977).

Biotinidase Deficiency. Biotinidase deficiency presents with a median age of 3 months (Wolf et al. 1983a), but it may present in the second decade of life (Wolf et al. 1998). In earlier literature biotinidase deficiency was referred to as the later infantile form of multiple carboxylase deficiency (Wolf et al. 1983a, b) to distinguish it from the usual neonatal presentation of holocarboxylase synthetase deficiency. It is also possible for adults with profound biotinidase deficiency to remain asymptomatic, although those individuals would be predicted to be at ongoing risk for symptoms to arise at times of intercurrent infection or other stress. Such individuals have been ascertained because of abnormal results on newborn screening of their babies (Wolf et al. 1997).

The cutaneous lesions tend to be patchy (Bartlett et al. 1980; Thoene et al. 1981), in contrast to the total body eruption seen in holocarboxylase synthetase deficiency, or there may be severe generalized involvement of the skin with redness and desquamation. Concomitant mucocutaneous candidiasis is common. The alopecia may be progressive to alopecia totalis but is usually less than total.

Neurological manifestations of biotinidase deficiency tend to be indolent and significant. Ataxia is a prominent feature and may interfere with walking (Thoene et al. 1981). Seizures are common and may be the only obvious symptom (Salbert et al. 1993); they may be general or myoclonic or may present as infantile spasms. There may be developmental delay and neurodevelopmental regression. Stridorous breathing and apnea have been reported in some patients,

Table 14.1 Biotinidase deficiency

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	Valvulitis, mitral	±	++	++, *	*	*
CNS	Ataxia	±	+	++, *	*	*
	Bulbar dysfunction	±	±	+, *	*	*
	Developmental delay	±	+	++, *	*	*
	Seizures	±	+	++, *	*	*
Dermatological	Alopecia	±	+	++, *	*	*
	Skin rash	±	+	++, *	*	*
Digestive	Glossitis	±	++	+, *	*	*
	Stomatitis	±	++	+, *	*	*
Ear	Hearing loss	–	+	++, *	*	*
Eye	Corneal erosion	–	+	++, *	*	*
	Optic atrophy	–	±	+, *	*	*
Respiratory	Stridor, inspiratory	±	±	±, *	*	*
Routine laboratory	Lactate (P)	±	+	++, *	*	*
Special laboratory	3-Hydroxypropionic acid (U)	±	++	+++, *	*	*
	3-Methylcrotonylglycine (U)	±	++	+++, *	*	*
	C5-OH-Carnitine (P, B)	±	++	+++, *	*	*
	Methylcitric acid (U)	±	++	+++, *	*	*

*Expression of symptoms highly depends upon adequacy of and compliance with treatment

Table 14.2 Holocarboxylase synthetase deficiency

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	Valvulitis, mitral	++	+++	+++, *	*	*
CNS	Ataxia	±	++	++, *	*	*
	Bulbar dysfunction	±	±	+, *	*	*
	Developmental delay	+	++	+++, *	*	*
	Seizures	+	++	+++, *	*	*
Dermatological	Alopecia	++	+++	+++, *	*	*
	Alopecia	++	+++	+++, *	*	*
	Skin rash	++	+++	+++, *	*	*
Routine laboratory	Lactate (P)	+	+++	+++, *	*	*
Special laboratory	3-Hydroxypropionic acid (U)	+	++	+++, *	*	*
	3-Methylcrotonylglycine (U)	+	++	+++, *	*	*
	C5-OH-Carnitine (P, B)	+	++	+++, *	*	*
	Methylcitric acid (U)	+	++	+++, *	*	*

*Expression of symptoms highly depends upon adequacy of and compliance with treatment

may be a presenting sign, and may be expected to resolve with biotin treatment. The untreated disease may be fatal (Wolf et al. 1983a; Sander et al. 1980).

Visual and auditory neurosensory abnormalities have been reported in a considerable number of patients, often as late complications. Loss of visual function is associated with optic atrophy and appears to be encountered only in patients for whom diagnosis and treatment is delayed (Wolf 2011). Neurosensory hearing loss seems to follow the same pattern (Wolf 2011). Many of the neurological features of disease disappear in response to treatment with biotin, as do the cutaneous and metabolic features; but sensorineural abnormalities involving the optic and auditory nerves are among those which are not reversible once they have appeared.

14.5 Diagnosis

Biotinidase deficiency is diagnosed by enzyme assay. It is generally conducted as a fluorometric assay and routinely performed on bloodspots in newborn screening programs worldwide (Heard et al. 1986); serum or plasma samples may be assayed also, and that is usually done for confirmation. The enzyme defect can be demonstrated whether the patient takes biotin or not, and the objective is to make the diagnosis prior to other biochemical changes. In the event of delayed treatment, the first biochemical changes generally include elevation of blood lactate and urine 3-hydroxyisovalerate and 3-methylcrotonylglycine. The diagnostic findings of holocarboxylase synthetase

deficiency are similar in terms of organic acid changes, but enzymatic confirmation is more complicated. The assay may involve formation of acid-precipitable radiolabel from $H^{14}CO_2$ in the presence of apocarboxylases prepared from biotin-deficient rats (Burri et al. 1981), but that is a difficult assay to validate to clinical standards. Presumptive diagnosis may be made in fibroblast cultures which are grown in biotin-depleted media to check the activities of carboxylases (Feigenbaum et al. 2009). A practical solution may be to use p67, a peptide comprising the 67 C-terminal amino acids of propionyl-CoA carboxylase, as the substrate (Rios-Avila et al. 2011). Molecular methodology to document DNA mutations (Morrone et al. 2002; Pindolia et al. 2010) is increasingly practical as a primary diagnostic step, and molecular studies are recommended to confirm an enzymatic diagnosis.

14.6 Reference and Pathological Values

Urine organic acids reference values

Compound	Range (mml/mol creatinine)
Lactic acid	0–197
3-Hydroxyisovalerate	0–58
3-Hydroxypropionate	0–24
Propionylglycine	0–2
Pyruvate	0–22
3-Methylcrotonylglycine	0–2
Methylcitrate	0–5

Urine organic acids pathological values

Compound	Range (mml/mol creatinine)
Lactic acid	Varies (generally >300, often >1,000)
3-Hydroxyisovalerate	Varies (generally >100)
3-Hydroxypropionate	Varies (generally >40)
Propionylglycine	Varies (generally >10)
Pyruvate	Varies (generally >40)
3-Methylcrotonylglycine	Varies (generally >10)
Methylcitrate	Varies (generally >15)

14.7 Specimen Collection

Samples for biochemical diagnosis of biotin disorders

No.	Disorder	Metabolite analysis (OAs)	Enzyme assay	Molecular characterization
14.1	Biotinidase deficiency	U	S, P, F	B
14.2	HCS deficiency	U	F	B

Abbreviations: *U* urine, *P* plasma, *S* serum, *B* blood, *F* fibroblast, *HCS* holocarboxylase synthetase, *OAs* organic acids

14.8 Prenatal Diagnosis

Though feasibility of prenatal diagnosis of biotinidase deficiency by enzymatic assay activity in amniocytes was demonstrated as early as 1984 (Secor McVoy et al. 1984), prenatal diagnosis is rarely undertaken, probably because outcome is expected to be favorable with treatment. Prenatal testing of amniocytes and chorionic villi has yielded evidence of normal fetuses and heterozygotes (Pomponio et al. 1998; Chalmers et al. 1994). If disease-causing mutations have been identified in the family, it is recommended to use DNA-based methods if prenatal diagnosis is desired (Wolf 1993). In holocarboxylase synthetase deficiency, amniotic fluid at 16 weeks gestation showed methylcitrate and 3-hydroxyisovalerate to be only slightly elevated, but enzyme assay was diagnostic in amniocytes (Suormala et al. 1998) and may also be applied to chorionic villi (Thuy et al. 1999). Given the complexity of the enzyme assay for HCS, molecular analysis affords advantages (Malvagia et al. 2005).

14.9 Treatment

Supplementation with pharmacologic doses of biotin is the cornerstone of therapy. Doses of 5–20 mg daily are generally used. In most cases, patients respond quickly and most symptoms are reversible; when dosage is inadequate or is stopped due to error or noncompliance, symptoms may reappear. Currently, dosage of biotin in the range of 5–10 mg per day appears to be adequate and effective during childhood (Wolf 2010). Usually the dose is not changed, so with growth, the body mass-normalized dosage tends to decrease. To assure that the dosage is adequate and that the patient is in compliance, some have monitored urinary organic acids (3-hydroxyisovleric and 3-methylcrotonylglycine) and/or plasma acylcarnitines (C5OH-carnitine) (Wolf 2010). There is some concern arising from anecdotal reports of several females with biotinidase deficiency who have begun to lose hair when entering puberty, with reversal when the dose is increased to 15–20 mg from 10 mg.

Supplementation must be in the form of free biotin in biotinidase deficiency (as opposed to some formulations marketed in the health food industry which are derived from yeast extracts and are composed of biocytin). The dosage is determined only by the body's requirements for biotin, since the supplemented biotin does not interact directly with the biotinidase enzyme. In HCSD, however, there is a direct interaction at the biotin binding site of the enzyme, so the effectiveness may be determined by the concentration of biotin. A few cases have been encountered which have been incompletely responsive or unresponsive to biotin (Wilson et al. 2005; Feigenbaum et al. 2009; Morrone et al. 2002; Santer et al. 2003; Sakamoto et al. 1999) and those have

proven to correspond to mutations outside of the biotin binding domain (exons 4–8), resulting in decreased Vmax. However, most cases of HCSD have been found to alterations in Km and relatively normal levels for Vmax, so those are all responsive to high doses of biotin (Bartlett et al. 1980).

As opposed to HCSD, the rationale is not clear for using biotin to treat isolated deficiencies of the individual carboxylases (primary forms of propionic acidemia, 3-methylcrotonyl-CoA carboxylase deficiency, and pyruvate carboxylase deficiency). Since biotin is covalently bound to the apocarboxylases through the action of HCS, it is not easy to imagine a mutation in the apocarboxylase itself which would affect that process but which would also be remediated with higher biotin concentrations, since the reversible binding of biotin is supposed to be limited to its interaction with HCS. It is a common practice to conduct a trial of biotin in newly diagnosed cases of isolated carboxylase deficiency, and there is one mutation in methylcrotonyl-CoA carboxylase (R385S) which is reported to be biotin-responsive (Baumgartner et al. 2004), but a response to biotin supplementation is virtually never observed in isolated carboxylase deficiencies.

If there is an incomplete response to biotin in an individual case of HCSD, alteration of the diet may be indicated, to limit protein and provide supplements of carnitine (and possibly glycine) as appropriate, in the same manner that isolated carboxylase deficiencies are managed. In general, a complete response is expected with adequate amounts of biotin in most cases of HCSD and all cases of biotinidase deficiency; in such cases, dietary modification is not necessary.

14.10 Follow-Up and Monitoring

Adequacy of treatment may be confirmed with periodic monitoring of urine organic acids, to look for an increase in 3-hydroxyisovalerate, 3-methylcrotonylglycine, and related metabolites. Even in cases where a complete response is documented, it is a common practice to monitor organic acids annually.

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