The Biotin Cycle and Biotin-Dependent Enzymes

Biotin is a water-soluble vitamin that is widely present in small amounts in natural foodstuffs, in which it is mostly protein bound. It is the coenzyme of four important carboxylases, which intervene in gluconeogenesis, fatty-acid synthesis, and the catabolism of several amino acids (Fig. 24.1) [1]. Binding of biotin to the four inactive apocarboxylases, catalyzed by holocarboxylase synthetase, is required to generate the active holocarboxylases (Fig. 24.2). Regeneration of biotin first involves proteolytic degradation of the holocarboxylases, yielding biotin bound to lysine (biocytin) or short biotinyl peptides. Biotinidase releases biotin from the latter compounds, which are derived from endogenous and from dietary sources.

Fig. 24.1. Location of biotin-dependent carboxylases in intermediary metabolism. ACC, acetyl-CoA carboxylase; CoA, coenzyme A; LAC, lactate; MCC, 3-methylcrotonyl-CoA carboxylase; OAA, oxaloacetate; PC, pyruvate carboxylase; PCC, propionyl-CoA carboxylase; PYR, pyruvate. Full lines indicate one enzyme, and dotted lines indicate that several enzymes are involved. Sites of the enzyme defects are indicated by solid bars.

Fig. 24.2. The biotin cycle. For definitions of abbreviations, see Fig. 24.1 [2]
Two inherited defects in biotin metabolism are known: holocarboxylase synthetase (HCS) deficiency and biotinidase deficiency. Both lead to multiple carboxylase deficiency (MCD). In HCS deficiency, the formation of holocarboxylases is impaired. In biotinidase deficiency, biotin depletion ensues from the inability to recycle endogenous biotin and to utilize protein-bound biotin from the diet. As the carboxylases play an important role in the catabolism of several amino acids, in gluconeogenesis and in fatty-acid synthesis, their deficiency provokes multiple, life-threatening metabolic derangements, eliciting characteristic organic aciduria and neurologic symptoms. The clinical presentation is extremely variable in both disorders. Characteristic manifestations of MCD are metabolic acidosis, hypotonia, seizures, ataxia, impaired consciousness and cutaneous symptoms, such as skin rash and alopecia. Both disorders respond dramatically to oral therapy with pharmacological doses of biotin. Acquired biotin deficiency, which also causes MCD, is extremely rare.

Clinical Presentation

The characteristic manifestation of MCD is metabolic acidosis associated with neurologic abnormalities and skin disease. The expression of the clinical and biochemical features is variable in both inherited disorders [1]. While patients with HCS deficiency commonly present with the characteristic manifestations of MCD, patients with biotinidase deficiency show a less consistent clinical picture, particularly during the early stage of the disease. The onset in biotinidase deficiency may be insidious, and the manifestation is usually very variable, neurologic symptoms often being prominent without markedly abnormal organic-acid excretion or metabolic acidosis. Later-onset forms of HCS deficiency cannot be clinically distinguished from biotinidase deficiency, necessitating confirmation of the diagnosis by enzyme assay.

Holocarboxylase Synthetase Deficiency

Although HCS deficiency was initially termed early-onset MCD, recent experience shows that the age of onset of symptoms varies widely, from a few hours after birth to 6 years of age [1, 3]. Nevertheless, about half of the patients have presented acutely in the first days of life, with symptoms very similar to those observed in other severe organic acidurias, i.e., lethargy, hypotonia, vomiting, seizures and hypothermia. The most common initial clinical features consist of respiratory difficulties, such as tachypnea or Kussmaul breathing. Increasingly severe metabolic acidosis, ketosis and hyperammoniemia may lead to coma and early death. Patients with a less severe defect and later onset may also present with recurrent life-threatening attacks of metabolic acidosis and typical organic aciduria [4, 5]. Untreated early-onset patients and patients with a less severe defect may additionally develop psychomotor retardation, hair loss and skin lesions. The latter include an erythematous, scaly skin rash that spreads over the whole body but is particularly prominent in the diaper and intertriginous areas; alternatively, the rash may resemble seborrheic dermatitis or ichthyosis. Superinfection with Candida may occur. Disorders of immune function have been observed with decreased T cell count and impaired in vitro and in vivo response to Candida antigen. Episodes of acute illness are often precipitated by catabolism during intercurrent infections or by a higher protein intake.