Maple Syrup Urine Disease 1954 to 1993

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Summary: The clinical, molecular genetic and other biochemical aspects of branched-chain \( \alpha \)-ketoacid dehydrogenase defects are reviewed.

Interest in the branched-chain \( \alpha \)-ketoacid dehydrogenase (BCKD; EC 1.2.4.4) complex began with the clinical description, in 1954, of a family in which four of six infants died (Menkes et al 1954). A common characteristic feature was the odour of maple syrup in their urine, hence the name maple syrup urine disease (MSUD; McKusick 248600) (Menkes 1959; Westall et al 1957). This odour was attributed to the elevated presence of branched-chain amino acids and ketoacids in the body fluids, and suggested a metabolic block in the catabolism of these compounds (Dancis et al 1959). Other individuals with this phenotype were identified and family histories were consistent with an autosomal recessive inheritance pattern. MSUD, or branched-chain \( \alpha \)-ketoaciduria, appears in all ethnic groups with a general incidence near 1 : 200 000 live births (Danner and Elsas 1989). For inbred populations with a higher carrier frequency this incidence can rise to 1 : 176, as for the Mennonite community of North America (DiGeorge et al 1982). Affected individuals are placed on a protein-restricted diet in an effort to bring the plasma amino acid profiles towards normal and to eliminate the ketoaciduria (Danner and Elsas 1989).

A clinical definition of three forms of MSUD emerged depending on age of onset, plasma amino acid levels, and amount of residual enzyme activity. In classic MSUD, the infants present at birth with poor feeding, apnoea, ketoacidosis, seizures, plasma leucine between 1000 and 5000 \( \mu \text{mol/L} \) and <2\% of normal ability to decarboxylate leucine. The severe variant form presents in infancy to young adulthood with ataxia, failure to thrive, and mild ketoacidosis. Plasma leucine ranges from 400 to 2000 \( \mu \text{mol/L} \), with leucine decarboxylation between 2\% and 20\% of normal. The mild variant manifests between childhood and adulthood with intermittent ataxia and ketoacidosis during infections or high protein ingestion. The range for plasma leucine is 50–1000 \( \mu \text{mol/L} \) and leucine decarboxylation ability is between 2\% and 40\% of normal (Danner and Elsas 1989). In 1971, Scriver described a ‘thiamin-responsive’ form of MSUD, in which daily pharmacological doses of vitamin B\(_1\) enabled the individual to tolerate a higher-protein diet while maintaining normal plasma leucine and none of the other clinical hallmarks (Scriver et al 1971; Fernhoff et al 1985).

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By the early 1960s, it was shown that MSUD resulted from an inability to oxidatively decarboxylate the branched-chain α-ketoacids (BCKA). Confirmation of this blocked pathway was obtained from enzyme studies using peripheral white blood cells or cultured fibroblasts from patients with this clinical phenotype (Dancis et al 1960; Goedde et al 1967). This function was associated with the mitochondria within the cell and likened to the then newly described decarboxylation of pyruvate by a multienzyme complex. Since there are three branched-chain amino acids (BCAA) (leucine, isoleucine and valine), and therefore three α-ketoacids, it was suspected that three separate, substrate-specific complexes would be found. Certainly the existence of a separate complex for pyruvate and α-ketoglutarate decarboxylation enhanced this possibility, yet the combined effect on the three BCAAs in probands with MSUD spoke to a common factor being affected in the catabolism of the BCKAs. When the mammalian BCKD complex was finally isolated and purified, it became clear that a single complex handled all three branched-chain α-ketoacid substrates, and more recently was shown to also decarboxylate the α-ketoacids from methionine and threonine (Pettit et al 1978; Danner et al 1979; Heffelfinger et al 1983; Jones and Yeaman 1986; Ono et al 1987; Yeaman 1989). Interestingly, methionine and threonine are not elevated in plasma from MSUD probands.

BCKD is a constitutive multienzyme complex located on the matrix side of the mitochondrial inner membrane of mammalian cells (Yeaman 1986). The reaction products of CO₂, branched-chain acyl-CoA and NADH are produced in a 1:1:1 stoichiometry (Danner et al 1979). The activity of this complex regulates the flow of branched-chain amino acids used for energy production since this is the committed, irreversible step in the catabolic pathway. Tissue-specific variation in complex activity is regulated by addition or removal of covalently bound phosphate through the action of a substrate-specific kinase and phosphatase (Paxton and Harris 1984; Damuni and Reed 1987).

Branched-chain α-ketoacids are produced from parent amino acids by reversible aminotransferase activity (Yeaman 1986; Danner and Elsas 1989) and enter the mitochondria via a specific transporter protein (Hutson et al 1990). Physically the BCKD complex is composed of four protein molecules that interact to oxidatively decarboxylate their ketoacid substrates. Current data are consistent with 24 dihydrolipoyl acyltransferase (E2) subunits interacting to form the core of the complex (Reed and Hackert 1990; Dardel et al 1993). A covalently linked lipoic acid at lysine 44 of the mature protein forms the acceptor site for the branched-chain acyl group generated by the action of the decarboxylase (E1). E1 decarboxylase is a heterotetramer, α₂β₂ (Reed and Hackert 1990). The α subunit binds thiamin pyrophosphate (TPP) to create the active site for the ketoacid substrate and decarboxylation. In addition, serine 292 and 302 of the mature protein receive a phosphate from ATP in rendering the complex inactive (Cook et al 1983a,b; Paxton et al 1986). E1β is thought to aid in transferring the acyl group to E2, but a definitive role for this protein is yet to be established. The flavoprotein, lipoamide dehydrogenase (E3), is a homodimer that functions to reoxidize the reduced lipoate in E2 using NAD⁺ as the terminal electron acceptor (Reed and Hackert 1990). This same E3 protein is used in the pyruvate and α-ketoglutarate dehydrogenase complexes. Current theory holds that 12 E1 tetramers

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