Why regulation of branched chain amino acid oxidation is important.

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The branched-chain amino acids (BCAA; leucine, isoleucine, and valine) account for about 20% of our dietary protein and are required for protein synthesis, branched chain fatty acid synthesis, and neurotransmitter synthesis. The branched chain ketoacid dehydrogenase complex (BCKDC) is the most important regulatory enzyme in the catabolic pathways of the BCAAs. Activity of the complex is controlled by covalent modification with phosphorylation of its E1α subunits by a specific kinase (BDK) causing inactivation and dephosphorylation by a specific phosphatase (BDP) causing reactivation of the complex. Tight control of BCKDC activity is important for conserving as well as disposing of BCAAs. Phosphorylation of the complex occurs when there is a need to conserve BCAAs for protein synthesis; dephosphorylation occurs when BCAAs are present in excess. A mitochondrial protein kinase (BDK) that is specific for BCKDC has been cloned and characterized. BDK belongs to the same kinase family as the pyruvate dehydrogenase kinases. A specific BCKDC phosphatase (BDP) has also been reported that does not belong to the same family (PP2C) as the pyruvate dehydrogenase phosphatases. A novel mitochondrial PP2C phosphatase was recently cloned that may contribute to the regulation of BCKDC. The activity of the BCKDC is reduced markedly in rats fed a low-protein diet or treated with thyroid hormone but increased in starvation, diabetes, sepsis, cancer, uremia, infections, and inflammatory disease caused by endotoxin and cytokines. Reduced capacity to oxidize BCAA oxidation, as in Maple Syrup Urine Disease, results in excess BCAAs in the blood and profound neurological dysfunction and brain damage. Loss of control of BCAA oxidation, as in the BDK knockout (BKO) mice, results in growth impairment and epileptic-like seizures. The devastating effects of MSUD and the phenotype of the BKO mouse emphasize the importance of BCAA catabolism and its control for normal neurological function.