Branched-Chain Amino Acids: Enzyme and Substrate Regulation[1–3]

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Abstract

The three branched-chain amino acids (BCAAs) are the most hydrophobic of the amino acids and play crucial roles in determining the structures of globular proteins as well as the interaction of the transmembrane domains of membranous proteins with phospholipid bilayers. However, the three BCAAs do not behave identically. In terms of protein secondary structure, valine and isoleucine exhibit a definite preference for the β-structure, whereas leucine has a higher preference for the α-helix. Although mutation of one BCAA to another is commonly regarded as conservative, there are well-documented examples of such substitutions that have a significant effect on protein function. The occurrence of BCAA in nature is, therefore, attributable to their primary role in protein structure, not to their secondary metabolic roles. These functions are important for almost all proteins; therefore, BCAA commonly account for ~20–25% of most dietary proteins. Dietary BCAA largely escape first-pass splanchnic metabolism. The first steps in their catabolism are common to all three, involving the BCAA aminotransferase (BCAT) and branched-chain α-keto acid dehydrogenase (BCKD). Their further metabolism employs distinct pathways to different end-products (glucose and/or ketone bodies). However, the fact that the flux-generating step for the catabolism of the three BCAAs occurs at one of the common steps indicates that the production of these downstream products are not individually regulated and, hence, may not play important individual roles. The catabolism of the BCAAs is highly regulated by both allosteric and covalent mechanisms. BCKD is inhibited by phosphorylation and activated by dephosphorylation. Allosteric inhibition of the kinase by the branched-chain keto acids (BCKA) (particularly by α-ketoisocaproate) serves both as a mechanism for promoting the catabolism of excess quantities of these amino acids as well as for conserving low concentrations of these dietary essential amino acids. Cytosolic and mitochondrial isoenzymes of BCAT have been identified. They are thought to play an important role in brain neurotransmitter metabolism.