

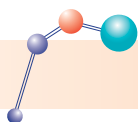
Newsletter Amino Acids Link News

Newsletter of Ajinomoto Co., Inc. Amino Acids Department

October 2005 Vol.12
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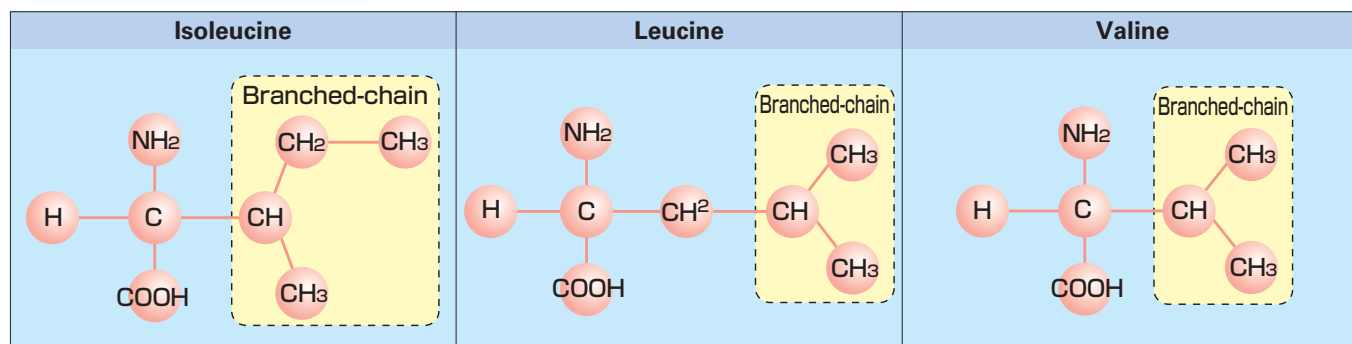
"Amino Acids of the 21st Century" (6) - Branched Chain Amino Acids (BCAAs)-

In this series, we herein present our research on the physiology and usefulness of Branched-Chain Amino Acids.

As often presented in the preceding issues of the journal, of the nine essential amino acids, valine, leucine and isoleucine, which have branched side chains, are called Branched-Chain Amino Acids (BCAAs).

BCAAs play important roles, particularly during exercise and in the maintenance and growth of skeletal muscle. BCAAs, which make up about 40% of the free essential amino acids in blood plasma, are used as an energy source during exercise as necessary, and play an important part in glyconeogenesis (a mechanism for reusing the glucose used for energy in muscle). In patients with liver cirrhosis, a significant decrease in plasma BCAA level may lead to malnutrition or seriously hepatic encephalopathy. It was found that the supplementation of BCAAs to such patients improved nutritional status and lengthened survival time.

Structure (structural formula)

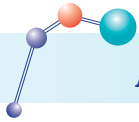


* Taste: Bitter

* Properties: Readily soluble in formic acid, poorly soluble in water, and practically insoluble in ethanol. Soluble in dilute hydrochloric acid.

Major effects and applications of BCAAs

Effects	Applications
1. Improvements in nutritional status	Transfusion, ingredient for oral nutritional supplements, sports supplements
2. Maintenance and growth of skeletal muscle	Transfusion, ingredient for oral nutritional supplements, sports supplements
3. Maintenance of stamina during exercise	Sports supplements
4. Drugs for the treatment of hypoalbuminemia	Therapeutic nutrients for hepatic failure



METABOLISM OF THE BRANCHED-CHAIN AMINO ACIDS

The three branched-chain amino acids are dietary essential amino acids that play a variety of roles in the body. These are described by Prof. John T. Brosnan of Memorial University of Newfoundland. It is clear that, in addition to their critical role as substrates for protein synthesis, these amino acids are important regulators of a variety of cellular functions. This article describes the role that these amino acids play in protein structure and discusses their metabolism, including the pathological consequences of a genetic impairment of their metabolism. It also deals with regulatory roles of these amino acids, in particular with recent work that has begun to reveal their effectiveness in promoting protein synthesis.

Introduction

The three branched-chain amino acids (BCAA), leucine, isoleucine and valine, are dietary essential amino acids which play critical roles in protein structure, metabolism and regulation. We know a great deal about the pathways by which the BCAA are metabolized as well as the regulation of these pathways, but we have a great deal to learn about their regulatory functions. Genetic defects in BCAA metabolism result in a serious inborn error of metabolism, Maple-Syrup Urine Disease (MSUD).

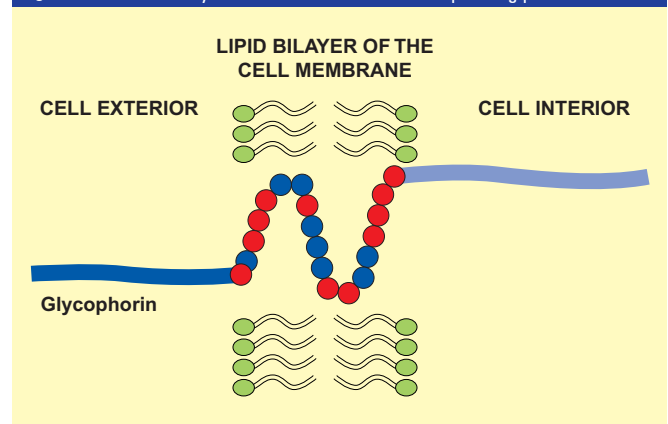
Roles of BCAA in Protein Structure

The most important function of the 20 fundamental amino acids that are incorporated into proteins is their role in the structure of proteins. Each one is uniquely suited to play specific roles in determining the structures of proteins. In the case of the three BCAA, their key property is their hydrophobicity. This means that their side-chains interact poorly with water. Therefore, in proteins, these amino acids are largely excluded from aqueous environments but they interact well with other hydrophobic molecules. In globular proteins they are largely found in the hydrophobic interior core where their interactions with other similar amino acids play a key role in determining the three-dimensional shapes of these proteins and, hence, of their functions.

The hydrophobic nature of the BCAA also provides a

means by which proteins can interact with other hydrophobic molecules, such as lipids. This is particularly important for membrane proteins as the interior of biological membranes is largely devoid of water. We now know that the parts of proteins that span membranes consist, very largely, of hydrophobic amino acids, and that the BCAA are particularly important. For example, glycoporphin, an important transport protein in red blood cells, completely spans the membranes of these cells. Of the 19 amino acids in the membrane-spanning sequence, 11 are BCAA (Figure 1). The importance of this function of the BCAA may be deduced from the fact that it is now apparent that fully 20-30% of our genes code for membrane proteins. Since these three amino acids cannot be synthesized by animals they must be provided in the diet. Table 1 gives the BCAA content of a number of common dietary proteins. The dietary requirement for the three BCAA amounts to about 35% of the total requirement for the essential amino acids. An adult, ingesting a typical North-American diet, would consume some 15-25 grams of BCAA per day.

Figure 1: Key role of BCAA in membrane-spanning proteins.



The circles represent amino acids in the membrane-spanning region of the red cell transport protein, glycophorin. The red circles are BCAA.

Table 1: Branched-chain amino acid content of some common dietary protein sources (mg amino acid / gram protein).

	Egg	Cow's Milk	Beef	Soy Isolate
Isoleucine	54	47	48	49
Leucine	86	95	83	82
Valine	66	64	50	48

● Metabolism of the BCAA

BCAA metabolism differs from that of the other amino acids in two important respects (Figure 2):

1. The first two steps in the oxidation of each of these three amino acids are catalyzed by two common enzymes (an aminotransferase which produces branched-chain α -keto acids (BCKA) and a dehydrogenase which metabolizes the BCKA),
2. The key regulated step in their oxidation, the BCKA dehydrogenase, is one of these common steps.

The body, therefore, metabolizes these three amino acids as a group. Indeed, their circulating concentrations tend to correlate closely with each other – when one branched-chain amino acid is elevated, so are the other two and vice versa. Subsequent to these two initial common steps, their metabolism proceeds to their individual end products – CO₂, glucose and acetoacetate. It should also be recognized that the BCAA are quite “energy-rich”, in that their oxidation produces considerable quantities of ATP, the energy currency of cells. Indeed, the oxidation of one molecule of leucine yields about the same quantity of ATP as does the oxidation of one molecule of glucose.

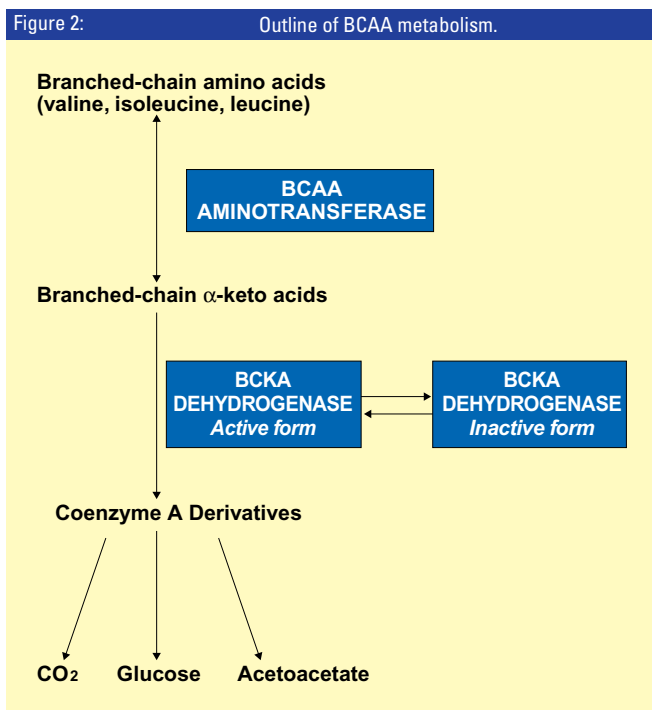
The regulation of the oxidation of the BCAA is very complex and centers on the BCKA dehydrogenase

which can exist in both active and inactive forms. Interconversion of these forms provides the basis for the control of BCAA oxidation. For example, when the dietary supply of these amino acids is in excess of that required for such key functions as protein synthesis, the BCKA dehydrogenase is converted to the active form which ensures their prompt oxidation. On the other hand, when it is important to conserve these essential amino acids (e.g. ingestion of a low-protein diet) this enzyme is largely converted to the inactive form. Exercise is associated with increased oxidation of BCAA, although these remain minor fuels compared with carbohydrate or fat.

Skeletal muscle is a major site for the catabolism of the BCAA. This represents an important difference between these and the other dietary amino acids which are primarily disposed of in the liver and intestine. Indeed, after a protein-rich meal, the BCAA account for a disproportionately high fraction of the increase in circulating amino acid levels. This postprandial increase in BCAA levels enables them to serve as regulatory signals for a variety of cellular processes.

● Maple-Syrup Urine Disease (MSUD)

MSUD (so-called because of a distinctive urinary odor) is a serious genetic disease of BCAA metabolism in which a mutation in the gene that encodes the BCKA dehydrogenase (Figure 1) produces a largely inactive enzyme. MSUD is found in about 1 per 200,000 newborns but an incidence as high as 1 in 200 is found in some U.S. Mennonite communities. A variety of different mutations have been reported and these produce diseases of varying severity. Some forms of MSUD respond to thiamine therapy (the vitamin, thiamine, is a co-factor for the BCKA dehydrogenase) but many do not. The clinical picture includes varying degrees of mental retardation, depending on the severity of the disease. The biochemical picture is characterized by very high circulating levels of the BCAA and the BCKA. In general, the higher the levels of these acids, the more severe the neurological symptoms. Early diagnosis and treatment are, therefore, critical. Newborn screening for elevated levels of BCAA is now routine in developed countries. A lifelong restriction of BCAA ingestion is a key component of the management of these patients. Since BCAA are ubiquitous in dietary proteins, the diet must be quite low in protein but supplemented with free amino acids to supply adequate nutrition. Recently, liver



transplantation has been shown to be an effective treatment for MSUD; however, the availability of livers for transplantation limits this option.

● Regulatory Roles of the BCAA

One of the new themes in nutrition research is the roles played by nutrients as regulatory (signaling) molecules. The BCAA present a number of examples of this phenomenon. The increase in circulating BCAA that occurs after a protein-containing meal is “sensed” by a number of different tissues and has important effects in these tissues. Thus, the BCAA serve as important signals to other tissues. Among the tissues that respond to BCAA concentrations are the brain and skeletal muscle.

Brain.

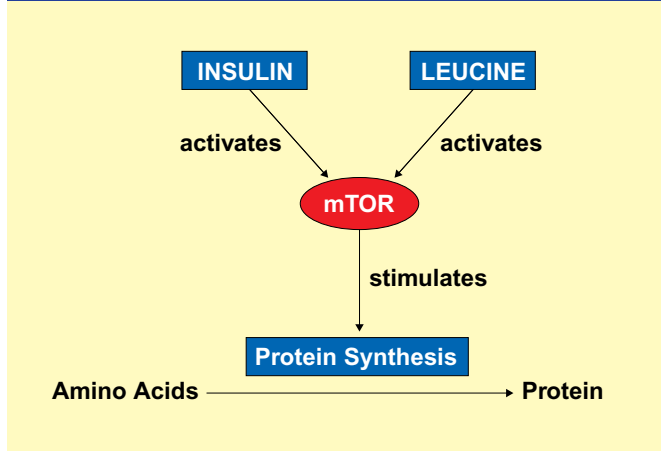
In addition to their roles in protein synthesis, amino acids play crucial roles in the brain. Glutamate is the most important excitatory neurotransmitter while the aromatic amino acids (tryptophan, tyrosine and phenylalanine) are precursors of the neurotransmitters serotonin, dopamine and nor-epinephrine. The uptake of amino acids into the brain involves their transport across the blood-brain barrier. Remarkably, the uptake of the large neutral amino acids is brought about by a single carrier, the large neutral amino acid transporter. The three BCAA as well as tryptophan, tyrosine and phenylalanine share this transporter; furthermore, they compete with each other for uptake. Elevated levels of BCAA can, therefore, reduce the brain uptake of the three aromatic amino acids and, as a consequence, decrease the synthesis of the three neurotransmitters derived from these amino acids. The functional consequences of this remains an active area of research.

Skeletal Muscle.

It is now clear that the BCAA, in particular leucine, regulate protein synthesis and degradation. This effect is separate from their role as amino acid substrates for protein synthesis. The regulation of protein synthesis is complex. The abundance of individual mRNA molecules is a critical determinant of the synthesis of individual proteins. However, there are also levels of regulation that affect the synthesis of many proteins in a tissue. These often occur via enhancement of the ribosomal steps of protein synthesis – the ribosome is the intracellular “factory” that translates the code inscribed in mRNA molecules into proteins with the correct sequence of amino acids. Perhaps the most potent

stimulus of protein synthesis is provided by the hormone, insulin. Insulin doesn’t enter cells but it initiates a cascade of events that reorients their metabolism. Much of this is brought about by a class of regulatory proteins known as protein kinases which phosphorylate (and alter the activity of) other proteins. In the case of the stimulation of protein synthesis it is clear that one of insulin’s intracellular targets is a protein kinase known as mTOR (Figure 3). We now know that leucine also activates mTOR, although the precise mechanism by which this occurs is yet to be discovered. This important finding provides a scientific basis for well-documented effect of leucine on protein synthesis as well as for its therapeutic potential to spare lean body mass during weight loss and ageing and to promote wound healing

Figure 3: Role of leucine in the stimulation of muscle protein synthesis.



The effects of insulin and leucine in activating mTOR involve a number of steps. The stimulation of protein synthesis by mTOR is also complex.

Dr. John T. Brosnan, Profile



Dr. John T. Brosnan received his B.Sc. and M.Sc from the National University of Ireland and his D.Phil, under the supervision of Professor Sir Hans Krebs, at Oxford University. He carried out post-doctoral research at the Banting and Best Department of Medical Research in the University of Toronto. Since 1972 he has been a faculty member in the Department of Biochemistry at Memorial University of Newfoundland, where he currently holds the rank of University Research Professor. He has served as President of the Canadian Society for Biochemistry and Molecular Biology and Chair of the Canadian Institute for Research in Nutrition, Metabolism and Diabetes. His research concentrates on amino acid metabolism, particularly during diabetes mellitus.