Branched Chain Amino and Keto Acids in Health and Disease

Editors:
S. A. Adibi, W. Fekl,
U. Langenbeck, P. Schauder

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Preface

Within the past few years there has been a large expansion of knowledge regarding the regulation of metabolism of branched-chain amino acids, and the effects of these amino acids and their metabolites on a range of metabolic reactions in various tissues of the body. This knowledge has already been used by clinical investigators to explain biochemical or physiological mechanisms of altered metabolism in common diseases, and to advocate the use of branched-chain amino acids and/or their ketoacid derivatives for therapeutic purposes. The first objective of this book is to bring together current reviews of these advances by basic and clinical scientists who have been the eminent leaders in this field. The editors hope that this book will be useful to the growing world-wide interest in metabolism and medical applications of branched-chain amino acids.

With any emerging new field there is always controversy and differing viewpoints. The field of branched-chain amino acids is no exception to this rule. The second objective of this book is to allow these controversies to be brought together to stimulate further research toward their resolutions.

While there has already been substantial progress in the metabolism of branched-chain amino acids and their involvement in metabolic reactions, much remains to be explored. The third objective of this book is to further stimulate basic and clinical research in this field.

Finally, under the auspices of the University of Göttingen School of Medicine and the Research Institute of Experimental Nutrition of Erlangen, an international symposium was held last October at the

Max-Planck Institute for Biophysical Chemistry in Göttingen. A select group of basic scientists and clinical investigators from different countries were invited to share observations and exchange ideas regarding their work on branched-chain amino acids in the intimate environment of this ancient and historic German city. The material covered in this book is largely, but not entirely, derived from the presentations made at this symposium.

S. A. Adibi
W. Fekl
U. Langenbeck
P. Schauder

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Nutritional, Physiological and Clinical Significance of Branched Chain Amino Acids

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It has taken more than a century for branched-chain amino acids to come of age in the world of biological and clinical science. These amino acids were discovered in the 19th century [1]. Leucine was obtained in impure form from cheese in 1819 by *Proust*, and in 1820 it was purified by *Braconnot*, who named it after the Greek word "Leukos", meaning white. Isoleucine was discovered and named by *Ehrlich* in 1904. Valine was discovered by *von Group-Besanez* in 1856. However, *Fischer*, in 1906, established its structure and its name.

The nutritional importance of branched-chain amino acids became established about the middle of this century by the results of studies of *Rose and co-workers* [1]. These studies showed that nitrogen balance in adults could not be maintained if any of the branched-chain amino acids was omitted from the diet. *Albanese* showed that the growth of human infants would be impaired if the diet was deficient in any of the branched-chain amino acids [1]. These studies led to the designation of branched-chain amino acids as essential amino acids, and to the formulation of daily requirements. These requirements, which form 46% of the daily need for essential amino acids, are currently used in designing chemically-defined diets for patients.

In 1954, *Menkes et al.* [2] discovered Maple Syrup Urine disease, a genetic disorder of impaired oxidative decarboxylation of branched-chain keto acids, which results in large concentrations of branched-chain amino and their keto acids in plasma. The disease is

characterized by mental and growth retardation and frequent bouts of metabolic and neurologic crises. It is rare for patients to survive past the second year. The discovery of genetic disorders of branched-chain amino acid oxidation promoted an interest in elucidating the pathways of oxidation of these amino acids. During the 1950's this problem was studied extensively. The results showed that branched-chain amino acids are first transaminated to their respective keto acids, and then through a series of oxidative reactions, these ketoacids are decarboxylated to acetoacetic acid and acetyl-CoA in the case of leucine, to propionyl-CoA and acetyl-CoA in the case of isoleucine, and to succinyl-CoA in the case of valine.

My own interest in branched-chain amino acids began in the mid-1960's when I was investigating the effect of diet on the plasma aminogram of normal human volunteers [3]. I found that among the amino acids, starvation uniquely increased the concentrations of all three branched-chain amino acids in plasma (fig. 1). Increases were evident within a day, reached a maximum by the second day, and persisted for seven to eight days. Resumption of a regular diet during the first week of starvation [4] or prolongation of starvation to two weeks [3] lowered the concentration of branched-chain amino acids to basal levels. In contrast to starvation, feeding healthy human volunteers a diet devoid of protein, but adequate in caloric content, lowered the plasma concentrations of branched-chain amino acids to below basal levels within one day (fig. 1). This reduction was more pronounced for valine than for leucine and isoleucine.

Reintroduction of protein into diet promptly returned the depressed levels of branched-chain amino acids to basal levels (fig. 1). These alterations in plasma concentration suggested that metabolism of branched-chain amino acids is under dietary control. In view of the absence of any knowledge of regulation of branched-chain amino acid metabolism by diet, it seemed that research in this area might yield useful information. Therefore, I began a series of experiments on various aspects of branched-chain amino acid metabolism, which have continued to the present day. As reviewed elsewhere [5], it is now clear that the increase in plasma branched-chain amino acid concentrations during brief starvation reflects the loss of body protein and the decrease in plasma branched-chain amino acid concentrations during protein deprivation reflects the conservation of body protein.

Since the early 1970's there has been growing interest in the studies of branched-chain amino acid metabolism [6]. The results of a number of studies have suggested that branched-chain amino acids may have important roles in regulating protein, carbohydrate, fat, and amino acid metabolism, and in certain clinical situations, branched-chain amino acids or their ketoanalogues may be used as therapeutic agents.

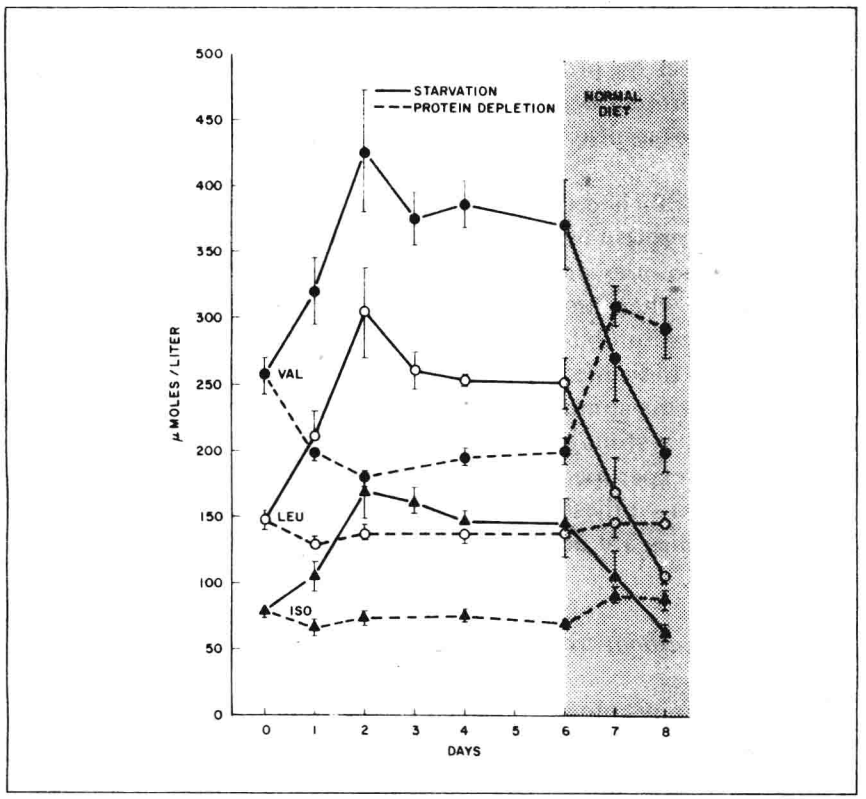

Fig. 1. Postabsorptive plasma concentrations of leucine (0-0-0), isoleucine (▲-▲-▲), and valine (●-●-●). Before (day 0), during (days 1-6), and after (day 7 and 8), each dietary deprivation in healthy human volunteers [4]. Each value represents the mean ± SEM of concentration values in six subjects.

Effect on Protein Metabolism

In addition to serving as a substrate for protein synthesis, branched-chain amino acids play a role in protein metabolism. For example, there is stimulation of protein synthesis and inhibition of proteolysis in muscle preparations when branched-chain amino acids are added to the incubation or perfusion medium [7–10]. This effect is unique to branched-chain amino acids since other amino acids do not have a similar effect [8]. In fact, among the branched-chain amino acids, the effect appears to be largely that of leucine [8]. Catabolism of leucine is not required for its effect on protein synthesis, but is required for its effect on protein degradation. For example, prevention of transamination of leucine to α-ketoisocaproate does not block the stimulatory effect on protein synthesis, but does abolish the inhibitory effect on protein degradation [11]. Therefore, α-ketoisocaproate or its metabolites appear to be responsible for the latter effect of leucine.

Although branched-chain amino acids also have an anabolic effect on hepatic protein metabolism, their effect on this tissue does not appear to be unique, since other amino acids have a similar effect [12]. However, when amino acids were individually tested, leucine was the strongest inhibitor of proteolysis in perfused rat liver [13].

In contrast to firm evidence in vitro, there is conflicting evidence in vivo that leucine stimulates muscle protein synthesis. Some reports have described a stimulatory effect [14] while others have not [15]. Differences in experimental design, such as the methods used to investigate protein synthesis, may have accounted for the varied results. Additional studies are needed to resolve this problem.

Effect on Carbohydrate Metabolism

Leucine in physiological concentration inhibits glucose oxidation by in vitro preparations of skeletal muscle and heart of fasted rats [16, 17]. Apparently, this effect is far more pronounced in the muscle preparation of fasted than fed rats. The mechanism of inhibition does not involve alteration in glucose uptake or glycolysis, but seems to include inhibition of pyruvate oxidation [16, 17]. Although all three branched-chain amino acids inhibit muscle oxidation of pyruvate,