Characteristics of alteration in protein metabolism in critical illness

The *in vivo* alterations of protein kinetics have well been studied in patients with thermal injury,[3,13–15] which could serve as a model of critical illness (Fig. 1). Accelerated muscle protein catabolism after thermal injury has been shown to persist for months.[16] The principal defect is an accelerated rate of protein breakdown, and a failure of protein synthesis to increase that sufficiently occur to compensate.[16] It has been believed that the breakdown of muscle protein is a major contributor to the overall catabolic responses in protein metabolism,[17,18] because muscle tissue is the largest organ among the organs in the body in which body protein is stored. Therefore, the improvement of protein kinetics in muscle tissues has been the target in the nutritional support to prevent the loss of body protein. Despite the fact that a variety of nutritional support has been clinically used, none of the treatment has been successful to sufficiently restore body protein and for amino acid and protein kinetics to be normalized. Although the use of total parenteral nutrition (TPN) results in a decrease in the protein loss that accompanies critical surgical illness, only a minority of patients are rendered anabolic.[19–21] Although the use of TPN results in a marked increase in whole body protein synthesis,[20,21] and as a result of a major decrease in the rate of net protein loss,[19] these patients remain in a state where net protein loss continues albeit at a slower rate than in the absence of TPN. One important reason of the inability for protein kinetics to be normalized is that the mechanism by which muscle protein catabolism occurs in patients with critical illness is not well understood. Furthermore, mediators of the increased rate of protein catabolism have not yet been identified. Although a number of hypotheses have been proposed in the past years,[14,22–24] none have been verified to explain the alteration in protein catabolism in critical illness.

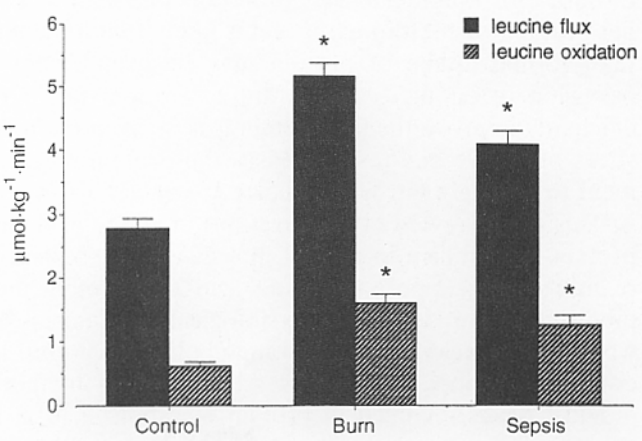

Fig. 1 Alterations of protein and amino acid metabolism in severely-burned patients. Parameters for protein and amino acid kinetics were obtained using a continuous infusion of leucine labeled with stable isotope. Leucine flux and leucine oxidation remarkably increased in burn and sepsis as compared with control (*$P < 0.05$ vs. Control). (From Ref. 14 with some modifications)

Methodological issues involved in the measurement of protein metabolism

Nitrogen balance studies: Nitrogen balance technique has been widely used as a gold standard for determining the balance between protein synthesis and breakdown at the whole body level.[25] Although this technique requires no unprovable assumptions, the interpretation of N-balance data is not as straightforward as would seem from its underlying principle. Hegsted[26] collated nitrogen balance data and concluded that there is a systematic error inherent in the way N-balance studies are performed. At protein intakes being above basal requirements, there is an apparent retention of approximately 20% of the extra nitrogen intake. In addition, this technique does not account for excretions of nitrogen from expired breath and sweat as a form of ammonia.

[^{15}N]glycine method: Constant infusion of ^{15}N-glycine is a method that was first used by Picou and Taylor-Roberts in 1969[27] and has subsequently been used by a number of investigators. Among the assumptions that are needed to make for this method, the most practical problem is that when ^{15}N-glycine is infused without priming of amino acid and urea pools, as many as 30 to 40 hours may be necessary for obtaining a plateau of urinary urea. Likewise, since different tracer methods involve problems and need particular assumptions, these should be accounted for the appropriate interpretation of the results. Over the past 50 years, the study of amino acid and protein metabolism has been the predominant area of application of stable isotopic tracer methodology. This in part reflects the fact that ^{15}N is a convenient stable isotope of nitrogen (the essential component of amino acids), and there is no other appropriate radioactive tracer of nitrogen.

Urea kinetics as a model for net protein catabolism

Net protein catabolism is also reflected by the measurement of urea production using [$^{15}N_2$]urea.[28] Net protein breakdown involves the oxidation of amino acids. In this process, the carbons of the amino acids are excreted in the breath as CO_2, leaving nitrogen for disposal. The nitrogen produced in peripheral tissues is transported to the liver primarily in the forms of