Changes in IGF-I and its binding proteins in critically ill conditions

Another possible mechanism responsible for an increased net protein catabolism is the marked depression in the circulating concentration of insulin-like growth factor I (IGF-I), an important anabolic hormone, after multiple mechanical injuries[74] and thermal injuries.[74–79] Resistance to the anabolic effects of growth hormone has also been reported, especially in patients with the most severe injury.[80] These evidences may provide a rationale for the exogenous administration of GH and/or IGF-I, which have been reported to increase nitrogen retention and to help preserve lean body mass after burn injury.[72,81,82] Thus, absence of positive modulator is likely to be central to the derangement in protein metabolism observed in critically ill conditions. However, IGF-I exists in plasma with several binding proteins, which forms IGF-I and its binding protein (IGFBP) complex. Therefore, the complexity of protein bindings influences the availability and bioactivity of IGF-I. We have recently shown using A-V balance study that there is a net uptake of IGF-I and IGFBP in burned patients,[83] which may partially explain a decrease in serum IGF-I concentration in burned patients.[83] Despite the fact that further increase in IGF-I uptake is noted in response to continuous infusion of insulin, arterial IGF-I concentration increased, suggesting that insulin infusion stimulates IGF-I production. Serum concentrations of IGFBP-1, -2, -3 and -4 are also altered in burned patients.[83] IGF-I is associated with IGFBP-3 and acid labile subunit, forming ternary complex, which may be an important mechanism by which serum IGF-I is regulated.[84] Thus, complex mechanism regulating IGF-I exists and it is not fully elucidated.

Effect of exogenous anabolic hormone administration

Since the report described by Wilmore *et al.*[85] demonstrated that growth hormone increased nitrogen retention in patients with thermal injuries and receiving adequate calories and nitrogen, multiple studies have confirmed over the past 25 years the usefulness of anabolic hormone in reducing the negative nitrogen balance associated with severe protein loss.[14,72,78,85–90] Insulin is the most important anabolic hormone liberated from pancreatic islet cell and has a tremendous effects on the regulation of substrate and protein metabolism. The physiological response of amino acid and protein metabolism to insulin has well been known in normal volunteers.[36,43,91] Insulin also improves nitrogen balance in traumatized patients.[46,92]

Furthermore, insulin stimulates amino acid transport.[93] *In vitro* and *in vivo* experiments have shown that insulin stimulates sodium-dependent system A amino acid transporter, in which alanine is the major substrate that has a large transmembrane concentration gradient.[94–99] Recent study indicated that long-term high-dose insulin infusion associated with enteral feeding markedly stimulates transmembrane amino acid transport in skeletal muscle, resulting in the improvement of amino acid and protein balance in skeletal muscle in severely-burned patients.[72] These results have provided an insight into the mechanism ivolved in the regulation of the balance of amino acid and protein kinetics in critically ill patients.

Summary

It has been long time since the alterations of protein kinetics in critical illness was reported, and various attempts in administering energy substrates and/or nutrients have been made to improve negative protein balance. However, none of the nutritional supports available so far have completely curtailed negative protein balance. Administration of anabolic hormone associated with energy substrates seems to be the most effective means available that efficiently improve protein kinetics. Although the mechanisms of alteration of protein kinetics have not been fully understood and none of the factors that directly regulate protein kinetics in critical illness have been identified, recent studies using tracer method have enable us to elucidate the mechanism involved in the alterations seen in critical illness. The impairment of amino acid transport in skeletal muscle may explain some aspects of the unresponsiveness of amino acid and protein kinetics to the administration of energy substrates and/or amino acids. Although it may not be conceivable to explain the alteration of protein kinetics by a single factor, several mechanisms and factors that are mainly responsible for the alterations of protein kinetics will be clarified in the future. Metabolic study using stable isotope tracers is an essential tool for *in vivo* quantitative evaluation of protein and amino acid kinetics.

Acknowledgments: The author thanks Drs. Takahiko Funabiki and Masahiro Ochiai (Professors of the Department of Surgery Fujita Health University, Toyoake, Aichi, JAPAN) for critical review, which were valuable contribution to this review.

References

1. Shaw JH, Wolfe RR: An integrated analysis of glucose, fat, and protein metabolism in severely traumatized patients. Studies in the basal state and the response to total parenteral nutrition. Ann Surg 1989; 209: 63–72
2. Shaw JH, Wolfe RR: Energy and protein metabolism in sepsis and trauma. Aust N Z J Surg 1987; 57: 41–47
3. Wolfe RR, Durkot MJ, Allsop JR, Burke JF: Glucose metabo-