individual cytokine.

Impaired transmembrane amino acid transport

The failure of response of critically ill patients to nutritional support alone especially on protein metabolism has not been fully explained by a single theory for a long period of time. Although the prevention of body protein loss in the skeletal muscle has been the primary goal of the nutritional support, the thesis that inward amino acid transport is impaired in critical illness is the hypothesis that might explain the inability of nutritional support alone to improve the nutritional status of critically ill patients. This thesis has been supported by the results of recent studies in which inward amino acid transport via system A was inhibited in muscle from septic rats.[64] Furthermore, incubation of fibroblasts with tumor necrosis factor significantly decreased inward system ASC-mediated glutamine transport activity.[65] A reduction in the rate of inward transmembrane transport of amino acids could potentially leads to net protein catabolism. It has been demonstrated that free amino acids used for protein synthesis intracellularly are derived from two sources, protein breakdown and transmembrane amino acid transport from plasma to intracellular compartment of tissue cells such as skeletal muscle cells.[66] When free amino acid influx from plasma compartment to intracellular pool is decreased, a higher-than-normal rate of protein breakdown is required to maintain normal concentrations of amino acids in the intracellular pool. This is possible, since the intracellular amino acid concentration apparently regulates muscle protein catabolism at least to some extent.[67] If such an increase in protein breakdown occurred, corresponding increase in protein synthesis would not be likely, since there would not be an adequate increase in the availability of intracellular amino acids. This is based on the fact that intracellular amino acid concentration also appears to be a direct regulator of protein synthesis.[17]

We have recently demonstrated in normal dogs[68] and humans[66] that more than half of free intracellular amino acid pool used for protein synthesis is derived from intracellular protein breakdown and the rest is derived from plasma through the transmembrane amino acid transport. These evidences have been based on the three-compartment model we have recently developed in our laboratory.[68] In physiological circumstances, the rates of amino acid transport in skeletal muscle were measured and it was found that the rates were different dependent on the amino acids. After exercise, the rates of amino acid transport were significantly increased and were associated with the increased rate of protein synthesis.[69] This evidence suggests that intracellular free amino acids that are required for the increased rate of protein synthesis in skeletal muscle are provided by the increased rate of amino acids in plasma that are transported by the transmembrane amino acid transport mechanism in cell membrane of the skeletal muscle. The rates of amino acid transport of skeletal muscle have been examined in burned patients.[70–72] These studies clearly demonstrated an impairment of amino acid transport in skeletal muscle in burned patients, which may partially explain the negative protein balance and a loss of skeletal muscle mass in burned patients (Fig. 4). It has been shown that increased rates of protein breakdown and protein synthesis occur in the whole-body level[14,73] and these alterations are attributable to the increased rates of protein breakdown and synthesis in skeletal muscle,[70] since skeletal muscle is the largest organ for the body protein store. Due to an impairment of transmembrane inward amino acid transport in burned patients, free amino acid supply from plasma is decreased, despite larger quantity of free amino acids required for the increased rate of protein synthesis. The impairment of amino acid transport was not improved by the excessive calorie intake with enteral feeding[71] or by the short-term administration of insulin. Long-term pharmacological dose of insulin associated with high-carbohydrate enteral feeding improved the rate of amino acid transport.[72] Although an impairment of amino acid transport in severely-burned patients is an important mechanism of negative protein balance of skeletal muscle, the question as to whether this mechanism could be extrapolated to other critically ill conditions remains to be solved.

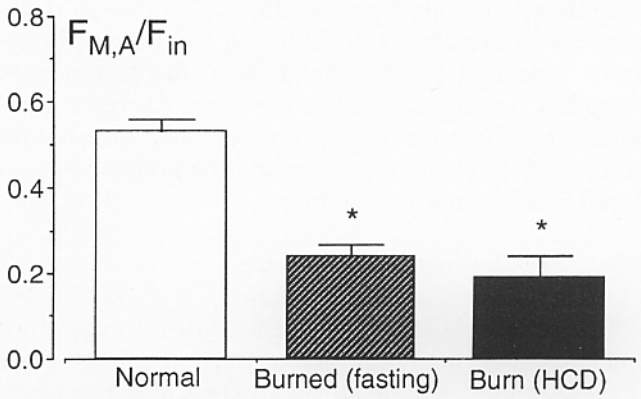

Fig. 4 Impaired amino acid transport of the skeletal muscle in severely-burned patients, which could be an important mechanism of negative protein balance of skeletal muscle that usually seen in severely-burned patients. $F_{M,A}/F_{in}$ (a fraction of phenylalanine transported from plasma into skeletal muscle cells in the total phenylalanine that flows into the leg) is used as an indicator of the rate of amino acid transport (*$P < 0.05$ vs. Control). (From Ref. 71 with some modifications)