Interorgan Relationships in Amino Acid Metabolism and Gluconeogenesis

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Regulation of protein degradation in skeletal muscle

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Protein balance in rat muscles incubated in vitro is influenced by the supply of insulin, leucine and various hormones at physiological concentrations (0.1–0.5 mM) (Goldberg & Chang, 1978; Goldberg et al., 1980). Leucine, but no other amino acid, stimulates protein synthesis and inhibits protein breakdown in this tissue. Metabolism of leucine is necessary for its inhibitory effect on proteolysis but not for the stimulation of protein synthesis. Thyroid hormones promote both protein synthesis and stimulate breakdown. This acceleration of catabolism is responsible for the muscle wasting in hyperthyroidism. Co-ordinate with the effects of thyroid hormone is its inhibitory effect on proteolysis but not for the stimulation of protein synthesis.

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Muscle protein degradation and amino acid metabolism in human injury

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The classical studies by Sir David Cuthbertson and his colleagues (for review see Cuthbertson & Tilstone, 1969) have demonstrated both in man and experimental animals that trauma is associated with increased loss of nitrogen in the urine (mainly as urea), and that the extent of the urinary excretion is related to the severity of the injury. This loss of nitrogen is due to an increase in protein degradation and/or a decrease in protein synthesis. Measurements of protein turnover in man have shown that moderate and controlled trauma (i.e. elective surgery) results in a decrease in protein synthesis with no significant change in the rate of protein degradation (O'Keefe et al., 1974; Crane et al., 1977). In more severe injury (e.g. multiple fractures, burns) the rate of protein degradation is increased.

An important source of the increase in nitrogen excreted in urine after trauma is amino acids released from muscle protein. This contribution is concerned with a brief discussion of three of these amino acids: 3-methylhistidine, a marker for myofibrillar-protein breakdown; alanine, an important gluconeogenic precursor; leucine, a branched-chain amino acid that is a potential respiratory substrate for muscle and that may also have a specific role in the regulation of protein synthesis.

3-Methylhistidine

3-Methylhistidine, a constituent of the muscle myofibrillar proteins, actin and myosin (Asatoor & Armstrong, 1967; Johnson et al., 1967), is formed by methylation of histidine residues already incorporated into peptide chains. When proteins containing 3-methylhistidine are degraded, the 3-methylhistidine released (unlike other amino acids) cannot be re-utilized for the synthesis of new proteins and is quantitatively excreted in the urine (Young et al., 1972; Long et al., 1975). Thus urinary 3-methylhistidine is ideally suited as a specific marker for the breakdown of myofibrillar protein in muscle.

There are, however, problems to its use as an index of myofibrillar degradation (for a review see Ward & Armstrong, 1967). The diet can make an appreciable contribution to urinary 3-methylhistidine, because flesh-containing foods have a significant content of 3-methylhistidine (M. Elia, A. Carter & R. Smith, unpublished work), and therefore where possible experiments should be carried out on subjects eating a flesh-free diet or, failing this, a diet where the 3-methylhistidine content is kept constant.

A moderate increase (40%) in excretion of 3-methylhistidine has been reported after elective surgery (Gross et al., 1978), and it is unlikely that this is due to the decreased food intake in the post-operative period because complete starvation decreases the excretion of 3-methylhistidine (Young et al., 1973). Accidental injury (multiple fractures) markedly increases (by 150%) the rate of 3-methylhistidine excretion (Williamson et al., 1977) in certain patients, suggesting that in this situation degradation of myofibrillar protein is greatly increased. Interestingly, there is not a close correlation between injury severity and excretion of 3-methylhistidine (Oppenheim et al., 1980). Measurement of urinary 3-methylhistidine does not, however, distinguish between increased protein degradation in injured and normal muscle.