Alterations in skeletal muscle protein metabolism

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Muscle protein is continually synthesised and broken down with a turnover rate in humans of 1–2% per day . Under normal circumstances, synthesis equals breakdown and muscle bulk remains constant. Physiological stimuli that promote net Carl Ferdinand Cori , 1896–1984, and his wife Gerty Theresa Cori MI, USA, were awarded a share of the 1947 Nobel Prize for Medicine. amino acid concentration) and exercise. Paradoxically , during exercise, skeletal muscle protein synthesis is depressed, but it increases again during rest and feeding. During the catabolic phase of the stress response, muscle wasting occurs as a result of an increase in muscle protein deg - radation (via enzymatic pathways), coupled with a decrease in muscle protein synthesis. The major site of protein loss is peripheral skeletal muscle, but it also occurs in the respiratory muscles (predisposing the patient to h ypoventilation and chest infections) and in the gut (reducing gut motility). Cardiac mus - cle appears to be mostly spared. The predominant mechanism involved in the wasting of skeletal muscle is the ATP-depen - dent ubiquitin–proteasome pathway (Figure 1.4), although the lysosomal cathepsins and the calcium–calpain pathway play facilitatory and accessory roles . Under extreme conditions of catabolism (e.g. major sepsis), urinary nitrogen losses can reach 14–20 /uni00A0 g/da y; this is equiv - alent to the loss of 500 /uni00A0 g of skeletal muscle per da y . Muscle catabolism cannot be inhibited fully by providing artificial nutritional support as long as the str ess response continues. - Hyperalimentation (excess feeding beyond requirements) was once in vogue to try and match the large losses, but it is now). recognised that h yperalimentation represents a metabolic stress in itself and that nutritional support should be at a mod - est level to attenuate rather than replace energy and protein losses. Treating underlying sepsis adequately is fundamental to limiting protein catabolism and is an essential part of e ff ective nutritional support. This includes searching for and treating recurrent septic episodes in the critically ill. Clinically , a patient with skeletal muscle wasting will expe - rience weakness, fatigue, reduced functional ability , decreased quality of life and an increased risk of morbidity and mortal - ity . In critically ill patients, muscle w eakness may be further worsened by the development of critical illness myopathy , a multifactorial condition that is associated with impaired ex citation–contraction coupling. Figure 1.4 , 1896–1957, Professors of Biochemistry , Washington University Medical School, St Louis,

Myo /f_i brillar protein Caspases, cathepsins and calpains Ubiquitinated protein Amino acids E1, E2, E3 AT P Tripeptidyl peptidase Ubiquitin 26S proteasome Oligopeptides AT P Substrate unfolding and proteolytic cleavage 19S 20S AT P The intracellular effector mechanisms involved 19S in degrading myo /f_i brillar protein into free amino acids. The ubiquitin–proteasome pathway is a complex multistep pro

cess. ATP , adenosine triphosphate; E1, ubiquitin-activating enzyme; E2, ubiquitin-conjugating enzyme; E3, ubiquitin ligase.

Skeletal muscle wasting /uni25CF /uni25CF /uni25CF /uni25CF

Provides amino acids for the metabolic support of central organs/tissues Is mediated at a molecular level mainly by activation of the ubiquitin–proteasome pathway Is inevitable to some degree but is prolonged by sepsis in particular Can result in immobility and contribute to prolonged recovery, poor healing, hypostatic pneumonia and death if prolonged and excessive

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