Manipulating the metabolic response to injury

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In this short review we will concentrate on just one of the features of the metabolic response to injury (classified as accidental trauma, injury or sepsis) which are collectively known as the 'flow' phase. These include an increase in energy expenditure (hypermetabolism), changes in substrate utilisation (insulin resistance) and the focus of this chapter muscle wasting or catabolism. It is recognised that the three features are interrelated, for example insulin is believed to be an important factor in controlling amino acid flux in skeletal muscle and increasing environmental temperature which may reduce flow phase hypermetabolism has been shown to reduce postoperative nitrogen excretion (a marker of protein catabolism). However, we will concentrate on muscle wasting and refer the reader to other reviews on insulin resistance and metabolic rate.

Muscle wasting

Cuthbertson in his pioneering studies of the metabolic responses to injury noted an increase in urinary nitrogen excretion which he interpreted as reflecting protein breakdown. In starved patients after elective abdominal surgery, nitrogen losses accounted for a smaller proportion of the energy deficit than did fat loss, but with increasing severity of injury and sepsis loss of lean tissue predominates. In patients admitted to intensive care following either severe trauma or sepsis, there were progressive losses of 17% in water, 16% total body protein and 19% total body potassium over 21 days. Such losses of lean body mass (whole body water and protein) of almost 1% per day of illness are far greater than can be accounted for by bed rest alone.

The major site of this protein loss is skeletal muscle. Muscle biopsy studies in the critically ill show losses of muscle protein approaching 2% per day and progressive fibre atrophy of all fibre types of between 1.5% and 13% of the fibre cross-sectional area per day. In those with multiple organ failure, the extent of muscle wasting bears little relationship to

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whether the patient is in positive energy or nitrogen balance. It should not be forgotten that the wasting is not restricted to skeletal muscle, the gut and the respiratory muscles are also involved. However, it seems that, at least, in severe sepsis cardiac muscle is preserved.

Muscle wasting is a balance between protein synthesis and degradation. After modest surgery there is a decrease in whole body protein synthesis rather than increased breakdown. Also, short-term starvation decreases skeletal muscle protein synthesis. With trauma, major surgery and multiple organ failure, both synthesis and degradation increase, the latter being more enhanced. Different tissues and organs respond differently during the course of an illness; for example, the liver and immune system show marked increases in protein synthesis following trauma. Tissue protein synthesis in the critically ill has now been characterised. The rate of muscle protein synthesis varies according to metabolic status and may be increased or decreased. The rate of protein synthesis in peripheral blood lymphocytes is increased, as is hepatic albumin synthesis.

It has recently been recognised that motor nerves are involved in multiple organ failure, compounding the difficulties of understanding the mechanisms that produce the wasting of muscle. A polyneuropathy, which involves a primary axonal degeneration of motor and sensory pathways has been described. It is associated with sepsis and multiple organ failure and is most frequently described in patients who have been ventilated for a number of weeks. In contrast muscle fibre atrophy is evident much earlier in the course of illness with necrosis being an unusual late event.

In studies of ICU patients, there is an early loss of myosin but relative preservation of the structural proteins (such as desmin) and increased lysosomal as well as ubiquitin proteolysis. The pathway responsible for the increased proteolysis in catabolic conditions is now recognised to be the ubiquitin-proteasome pathway that requires ATP and is stimulated by fasting, acidosis, trauma, sepsis, cancer and denervation. Activation of this pathway occurs within hours of the injection of endotoxin. It would appear that glucocorticoids are important in the control of proteolysis in muscle, but they also enhance the hepatic utilisation of the released amino acids. The chief factor opposing the catabolic effect of glucocorticoids is insulin. The response to sepsis or injury and the signal cascade of TNF and interleukins from activated macrophages and endothelial cells also stimulate the ubiquitin-proteasome pathway in muscle. In sepsis, providing protein in excess of 1.5 g/kg body weight/day does not improve the nitrogen balance. In eight septic ventilated patients, despite receiving parenteral nutrition of 2,700 kcal and 22.6 g nitrogen per day there was a loss of 1.5 kg protein with a gain of 2.2 kg fat and glycogen over 10 days.

There is good evidence for widespread and profound alterations in capillary endothelial activation in skeletal muscle of critically ill patients. There is a 60% increase in thickness of the endothelial cell...
and basement membrane without any reduction in the capillary lumen or evidence of vascular occlusion. However, the increase in endothelial and basement membrane thickness could compromise the blood–tissue interface. The endothelial swelling was characterised by increased von Willebrand factor (vWF) staining consistent with the increased vWF levels observed in the plasma in the critically ill.

These observations all point to a generalised involvement of muscle during sepsis and multi-organ failure. The causes of muscle wasting and weakness are multifactorial, including inadequate nutrition, neuropathic and myopathic processes, sepsis and intense cytokine and neurohumoral stimulation, drugs and immobility. Of the potential strategies for preventing or reversing muscle wasting, the most obvious would seem to be the provision of enough calories to ensure that the patients are in energy balance. However, it seems that even if calorie balance can be achieved net muscle catabolism continues. Thus other strategies have been suggested and a number of these will now be considered.

**Muscle stimulation**

The single feature common to all severely ill patients is the marked inactivity of their muscle. In otherwise healthy subjects, immobilisation of a limb is well known to result in muscle atrophy. In part this can be ameliorated by activity or electrical stimulation. It has also been suggested that muscle wasting in the severely ill can be reduced by similar means. What is not clear is whether it is the muscle contraction per se or the forces and stresses induced in the muscle that prevent atrophy. A reduction in gravitational stress (head-down tilt) in normal volunteers for 30 days has shown a number of structural changes in skeletal muscle which imitate some of the features seen in the critically ill.

In critically ill patients, the effects of passive stretching of muscle have been examined. One leg was passively stretched whilst the other leg acted as the control. To exclude the effect of voluntary contractile activity, the patients received neuromuscular blocking agents so that any forces on the muscle were strictly passive and not influenced by either central drive or stretch reflex activation. There was preservation of architecture in the stretched muscle with reduced protein loss and less fibre atrophy. This did not seem to involve stimulation of protein synthesis suggesting that proteolytic activity was reduced. Three mechanisms exist to translate mechanical force into cellular activity. Integrin receptors on the cell surface and the associated intracellular cytoskeletal microtubular system may permit direct transmission of the mechanical force from the extracellular matrix to intracellular protein synthesis (ribosomal or nuclear). Influx of Na⁺ and Ca²⁺ through stretch
activated ion channels with intracellular signal may initiate mechanotransduction. Second messengers, especially adenylate cyclase and phospholipase C from membrane bound enzyme complexes may stimulate early gene and cell replication. It has also been suggested that the changes in muscle may partly be mediated by the autocrine/paracrine action of IGF-I\(^{33}\). This study did not assess the influence of passive stretch on force generation and it is equally likely that the activity may have benefited connective tissue and proteoglycans rather than the contractile proteins. The striking preservation of the architectural structure of the muscle goes along with the concept of reducing proteolysis but it does not suggest whether the mechanism is acting directly on the muscle or indirectly by affecting the circulation and nutrient supply.

**Glutamine**

Following trauma or surgery, there is a marked acute and prolonged depletion of intracellular non-essential amino acids, notably glutamine\(^{10,34}\). This change is accompanied by increases in the essential branched-chain amino acids, phenylalanine, tyrosine and methionine.

Glutamine (Gln) accounts for nearly two-thirds of the free intracellular amino acid pool and thus is the most abundant amino acid in the body. Glutamine concentration is typically 0.6 mmol/l in plasma, but about 20 mmol/l in intracellular water in skeletal muscle. The large free pool and the wide distribution of its synthetic enzymes have meant that glutamine has been considered as a non-essential amino acid. In stress, it is released from skeletal muscle through activation of a special transport system (system N)\(^{35}\) and acts as an interorgan nitrogen and carbon transporter. It is an important energy source directly for many cells and indirectly as a major, and until recently underestimated, player in glycogen metabolism\(^{36}\). It is fundamental for protein synthesis where it donates nitrogen for the synthesis of purines, pyrimidines, nucleotides and amino sugars. Glutamine is also an important substrate for the synthesis of glutathione which acts as an endogenous scavenger with the ability to counteract oxidative injury from oxygen free radicals. Depletion of tissue glutathione has also been shown in the critically ill\(^{37}\) and appears more related to glutamine depletion than that of cysteine.

Important consumers of glutamine include the kidney, liver\(^{38}\), small intestine\(^{39}\) and cells of the immune system\(^{40,41}\). Since most of the glutamine that enters the body via protein in the diet is probably utilised by the gastrointestinal tract, the immune system (including the gut associated lymphoid tissue in gut failure) is probably dependent on supply from the liver, muscle and adipose tissue. Of these stores, skeletal muscle is the most important with the release of glutamine the key regulatory step for the
utilisation of glutamine by the immune system\textsuperscript{42,43}. Indeed, the same authors speculate that the increased proteolysis seen in sepsis and injury is to provide precursors for the synthesis of glutamine\textsuperscript{43}. There is also evidence that points to a role for glutamine in arginine–nitric oxide metabolism\textsuperscript{44} such that glutamine plays a more global regulatory role by modifying the endogenous inflammatory response, and/or by upregulating anti-inflammatory factors\textsuperscript{45}. The falls in plasma and skeletal muscle intracellular glutamine are thought to reflect a demand greater than can be met by endogenous supply. If these falls are reflected by impairments in immune system function, they could influence morbidity and mortality.

Many clinical studies of glutamine supplementation in less severely ill patients have shown preserved intestinal integrity\textsuperscript{46}, enhanced immune function\textsuperscript{47,48} and attenuation of the fall in muscle glutamine concentration and protein synthesis following surgery\textsuperscript{49}. If supplements are discontinued prematurely, however, intracellular glutamine levels fall again\textsuperscript{50}. In cachetic cancer patients, plasma glutamine is reduced in proportion to the extent of malnutrition\textsuperscript{51}. Furthermore, extraction of glutamine by the small intestine which is dependent on arterial glutamine concentration is decreased\textsuperscript{51}. The metabolism of glutamine by the small intestine is important to provide citrulline to serve as a precursor for arginine synthesis in the kidney. Intravenous glutamine increased mucosal glutamine in the depleted patients only\textsuperscript{52}.

There are few studies examining glutamine supplementation in the critically ill. Fully restoring plasma and intramuscular glutamine in the critically ill patient with 5 days of glutamine supplemented parenteral nutrition has proved difficult\textsuperscript{53}. This suggests that the exogenous glutamine is meeting the increased tissue demands. A limited dosing study in the critically-ill suggest that more than 21–28 g glutamine per day are required if sustained elevations in plasma glutamine are to be achieved\textsuperscript{54}.

There has been a prospective, block-randomised, double-blind study testing whether ‘all in one’ glutamine parenteral nutrition compared with isonitrogenous, isoenergetic control parenteral nutrition modified morbidity, mortality and cost at 6 months post intervention in the critically ill\textsuperscript{55}. Survival at 6 months was significantly better with glutamine parenteral nutrition (57% versus control 33%). Despite the improved survival in the glutamine group this did not, as might be expected, increase total hospital costs since the excess control deaths occurred later and had a significantly longer (and, therefore, costlier) postintervention stay and use of ICU. As a consequence, using a glutamine parenteral nutrition led to a 50% reduction in the total ICU and hospital cost when expressed per survivor. Further analysis showed that rather than preserving muscle mass the survival advantage may have been because exogenous glutamine ameliorated some of the immediate consequences of the lack of endogenous glutamine supply from a reducing
skeletal muscle pool. Thus, the greater the initial muscle mass the longer survival in critical illness before a critical protein reserve is reached. Nutrition may slow this process, and the addition of exogenous glutamine may replace the deficient supply from the declining muscle mass.

**Growth factors**

Complex alterations in the growth hormone/insulin like growth factor (GH/IGF) axis are thought to play an important role in the protein catabolism which complicates trauma, burns, sepsis and major surgical procedures. Although basal GH levels are sometimes increased, oscillatory activity is frequently attenuated and, in prolonged critical illness, blunted GH secretion has been shown to consist of a large number of small secretion bursts superimposed on basal secretion, probably in part due to changes in the hypothalamus. This reduction in pulsatile GH secretion seems to contribute to the fall in circulating levels of IGF-1, IGF-2, their major binding protein IGFBP-3 and its associated acid-labile subunit (ALS) which has been consistently described in the critically ill. These changes are associated with induction of a protease which decreases the affinity of IGFBP-3 for IGF-1 and, thereby, reduces the amount of IGF-1 carried in a relatively inert state in the IGFBP-3/ALS/IGF-1 high molecular weight complex. Induction of protease activity could, therefore, exacerbate catabolism by reducing the half life of IGF-1 in the circulation and increasing its clearance. Alternatively, protease activity might help to counteract catabolism by increasing the bioavailability of IGF-1.

Circulating levels of the GH independent binding protein IGFBP-1, which has a lower molecular weight and a relatively short half life, increase in response to traumatic or surgical injury and the normal inverse relationship between insulin and IGFBP-1 levels is lost. Similarly in endotoxaemia, plasma concentrations of small molecular weight IGFBPs (-1, -2, -4) rise, perhaps allowing increased transfer of IGF-1 across the vascular endothelium into the interstitial space where it is available to elicit a biological response. In keeping with these observations, caecal ligation and puncture in the rat leads to a reduction in hepatic IGF-1 and IGFBP-3 mRNA levels, whilst hepatic IGFBP-1 and IGFBP-2 mRNA levels rise. Recovery from critical illness is associated with an increase in circulating levels of IGF-1 and IGFBP-3, cessation of protease activity and a fall in plasma IGFBP-1 levels.

It seems, therefore, that the GH/IGF axis undergoes adaptive changes in response to serious illness, injury and starvation such that the indirect anabolic actions of GH mediated by IGF-1 are reduced while, at least in
the acute phase, raised basal GH levels lead to increased lipolysis and insulin antagonism. The fall in circulating IGF-1 promotes muscle catabolism, yielding amino acids such as glutamine (see above) for protein synthesis in rapidly dividing cells (e.g. gut mucosa and leucocytes) and for wound healing, whilst avoiding the hazards of hypolycæmia. Such changes might be of benefit in the short term by providing the patient with metabolic fuels at the cost of increased protein breakdown. However, if the changes persist they can lead to the severe muscle wasting and weakness discussed above.

Administration of GH or IGF-1, or a combination of the two might, therefore, be expected to attenuate the catabolic response to injury and enhance recovery. There are now a large number of studies demonstrating that supraphysiological doses of recombinant human (rh)GH (5–20 times the dose used in GH deficient adults) can increase circulating levels of IGF-1 and improve nitrogen balance in humans who are catabolic secondary to surgery, overproduction of glucocorticoids, pulmonary disease, burn injury, trauma, short bowel syndrome and AIDS. It was initially thought that GH would only exert a significant effect during the convalescent phase of acute illness, but administration of supraphysiological doses of rhGH has been shown to improve nitrogen balance even in the early phase of severe sepsis and trauma.

Administration of rhGH to patients who had undergone elective cholecystectomy resulted in neutral nitrogen balance with maintenance of skeletal muscle ribosome concentration and attenuation of the postoperative fall in muscle free glutamine. Whilst controls, who received TPN alone, remained in negative nitrogen balance with significantly decreased muscle protein synthetic ability and loss of up to 40% of muscle free glutamine. In a placebo-controlled, randomised study of 180 patients undergoing elective cholecystectomy treated with hypocaloric parenteral nutrition plasma albumin levels were maintained in those given a small dose of rhGH whereas they fell in the controls. This was associated with a significant rise in plasma GH, IGF-1 and insulin concentrations in the treatment group. Moreover, the incidence of wound infection was 17.2% in the control group compared with only 3.4% in the treatment group, possibly contributing to the significantly shorter length of hospital stay in those given rhGH.

In some studies, however, nitrogen balance was not improved by GH and another GH treatment failed to prevent muscle breakdown despite increased serum levels of GH, insulin, IGF-1 and IGFBP-3. On the other hand, in one study of trauma victims serum albumin levels were significantly increased by rhGH treatment.

There is only limited evidence that the improvement in nitrogen balance which can be achieved with rhGH is clinically useful. In children with burns, rhGH significantly reduced the length of hospital stay, probably...
largely as a result of accelerated donor site healing\textsuperscript{80}, whilst in surgical patients treatment with rhGH preserved hand grip strength\textsuperscript{61}. Improved ability to cough and shorter weaning times have also been reported\textsuperscript{64,81}. A 3 week course of rhGH improved maximal inspiratory pressure in patients with chronic obstructive pulmonary disease (COPD)\textsuperscript{66}, although a much shorter course of rhGH failed to increase muscle strength in patients with COPD\textsuperscript{67}, and, in a small controlled study of mechanically ventilated patients, treatment with rhGH was not accompanied by improved muscle strength or decreased weaning times, despite marked nitrogen retention\textsuperscript{82}.

The administration of growth hormone to critically ill patients is not without potential problems. Its anti-insulin effects are well documented\textsuperscript{83}, as are its lipolytic actions. The latter could increase plasma free fatty acid levels and result in fatty infiltration of the liver, micro-embolism, hypercoagulability, changes in membrane function, increased production of eicosanoids and increased susceptibility to cardiac arrhythmias. It may also be involved in the pathogenesis of insulin resistance, one of the features of the ‘flow’ phase.

Both GH and IGF-1 have a number of immunomodulatory effects on both lymphocytes and macrophages and may function as phagocyte-activating factors\textsuperscript{84,85}, enhancing the production of reactive oxygen intermediates and increasing lymphocyte activity. The experimental findings are, however, often conflicting. For example, whereas GH administration has been shown to enhance the interferon-gamma response to burns injuries and reduce mortality in mice infected with the herpes simplex virus\textsuperscript{86}, in the rat prior administration of GH, but not IGF-1, increases susceptibility to endotoxaemia\textsuperscript{87,88}. \textit{In vitro} studies have shown that treatment of mononuclear cells with GH inhibits endotoxin induced production of TNF and IL-1\textsuperscript{89} and GH treatment has been shown to blunt the increase in circulating TNF in response to endotoxin in calves\textsuperscript{90} and bacterial challenge in mice\textsuperscript{86}. In another study, GH was shown to worsen the metabolic acidosis and bleeding tendency in traumatised, septic piglets\textsuperscript{91} in association with reductions in portal blood flow, possibly combined with increased metabolic oxygen requirements\textsuperscript{91}. These latter changes might lead to increased translocation of bacteria and their cell wall components from the gut lumen.

As discussed above, glutamine requirements are markedly increased in critical illness and, as a result, both plasma and muscle levels of this conditionally essential amino acid may be profoundly depleted in catabolic states\textsuperscript{92}. The nitrogen sparing effect of GH, and the preservation of lean muscle mass, is associated with preservation of muscle glutamine levels and GH treatment prior to trauma in piglets has been shown to increase intestinal glutamine uptake\textsuperscript{93}. If glutamine mobilisation from muscle is prevented, less may be available to the immune system and other rapidly dividing cells and this could be detrimental.
Because these side effects are likely to be more frequent and serious when large doses of GH are given in an attempt to overcome the GH resistance seen in critically ill patients, there has been considerable interest in the potential of rhIGF-1 administration, either alone or in combination with smaller doses of rhGH, to attenuate the catabolic response.

Although initial investigations of IGF-1 administration in animals and human volunteers have often been encouraging, studies in catabolic patients have so far proved disappointing. Three randomised, placebo controlled, double blind studies have failed to demonstrate a protein sparing effect of rhIGF-1 in postoperative patients\textsuperscript{94-96}. Sandstrom and colleagues\textsuperscript{96} concluded that the failure to achieve nitrogen sparing could, in part, be due to the absence of supplemental amino acids in their patients who received only intravenous dextrose throughout the study. However, in both the other studies\textsuperscript{94,95} patients were receiving total parenteral nutrition.

In critically ill patients with systemic inflammation a single, small dose of rhIGF administered subcutaneously significantly increased circulating IGF-1 levels after 3 h but levels had returned to baseline by 8 h. An attenuated response was seen in the more severely ill patients associated with high levels of IGFBP-1, low levels of IGFBP-3 and the presence of marked protease activity. Some negative feedback was evident, as endogenous GH levels fell significantly 4—6 h following rhIGF-1 administration. There were no adverse effects attributable to rhIGF-1 administration\textsuperscript{97}.

When GH and IGF are given in combination they may have synergistic effects on protein anabolism\textsuperscript{98}. There may be several explanations for the enhanced efficacy of combination treatment. Insulin's anabolic properties are well documented and may differ in mechanism of action to those of GH. GH administered with IGF-1 counteracts IGF-1's hypoglycaemic and insulin lowering effects and thus maintains plasma insulin concentrations, thereby, augmenting the anabolic effects of the growth factors by allowing greater inhibition of proteolysis. Moreover, substantially higher serum IGF-1 concentrations are achieved with the combination, IGF-1 is stabilised in the ternary complex, its clearance is reduced and tissue IGF-1 levels (which may be more relevant than serum levels), are increased. The additive effect of the different mechanisms of action of GH (predominantly increasing protein synthesis) and IGF-1 (predominantly inhibiting proteolysis) may also contribute.

\textbf{β\textsubscript{2}-adrenoceptor agonists}

There is considerable evidence that β\textsubscript{2}-adrenergic agonists are potent anabolic agents in a number of species including farm animals and rodents\textsuperscript{99,100}. For example, agents such as clenbuterol and cimaterol reduce body fat content and increase lean tissue mass in animals fed either a normal or protein-deficient diet\textsuperscript{101,102}. They also reduce or restore protein
loss in animal models of scald injury, surgery, endotoxaemia and malnutrition. It has also been shown that clenbuterol-induced muscle fibre hypertrophy is accompanied by parallel increases in contractile strength. Whilst there are problems with the availability of many such agents for clinical use, the short-term administration (14 days) of a sustained release preparation of salbutamol has been shown to increase voluntary muscle strength in young men. However, their therapeutic potential in critical illness has yet to be explored.

Oxandrolone

Oxandrolone is a testosterone analogue with anabolic activity that has been used in the treatment of delays in growth and puberty in boys and Turner’s syndrome in girls. Its anabolic action has also been shown to be of benefit in patients with severe malnutrition and with alcoholic hepatitis. Recently, a prospective randomised trial in patients with severe burns has shown that oxandrolone combined with an increased protein intake significantly increased the rate of weight gain and improved subjective measures of muscle strength.

Conclusion

The muscle wasting associated with critical illness cannot be prevented/reversed by the provision of calories and nitrogen alone. The need to overcome this catabolic drive has lead to a number of trials of supplementing feeding regimens with, for example, either glutamine or growth factors. Whilst both have shown some benefit, there is no unequivocal evidence to support their use and the quest continues for other strategies. Oxandrolone and β-adrenergic agonists probably warrant further investigation as do agents that can modify the cytokine response to severe illness. Unfortunately, a limitation of such approaches is that they can have effects other than the preservation of muscle mass and function and, thereby, any potential benefit could be offset by a deleterious interaction with another homoeostatic system.

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