Metabolic response to sepsis and trauma

This review examines current knowledge regarding the metabolic responses to trauma and sepsis. The factors which may mediate the responses are discussed and the potential value of pharmacological or nutritional manipulation is reviewed.

Keywords: Metabolic response, sepsis, trauma

The accelerated breakdown of skeletal muscle following significant injury was first identified by Cuthbertson more than 50 years ago. He divided the response into a short-lived 'ebb' phase, corresponding to the period of hypovolaemia and sympathetic activity immediately after injury, and a more prolonged 'flow' phase which is characterized by a negative nitrogen balance. A catabolic state similar to the flow phase of trauma also occurs in patients with established sepsis, and many parallels can be drawn between the metabolic profile of the severely injured and septic patient. This article is a review of the present knowledge of the metabolic responses to trauma and sepsis. Contention persists over some aspects of the nature of these responses and the factors which mediate them, and data and interpretations of the polemical issues will be presented.

The consequences of a prolonged catabolic response are now seen more frequently as intensive care facilities prolong the survival of multiply injured and severely septic patients. Although modern techniques of enteral and parenteral nutrition are able to reduce the rate of consumption of protein and energy reserves it is not yet possible to achieve a positive nitrogen balance in severely stressed patients. The last section of this review discusses the impact of intravenous nutrition on the metabolism of septic and trauma patients and summarizes the results of experimental work with agents which promote protein conservation in this setting.

Mediators of the metabolic response to sepsis and trauma

It is well established that the neuroendocrine response to sepsis and trauma effects many of the observed changes in metabolism (Figure 1). More recent work has suggested that inflammatory mediators released from the wound itself or from a septic focus may also play a part in these changes. Despite extensive investigation there remains much conjecture about the nature of the link between tissue insult and the resultant metabolic response.

The neuroendocrine response

Injury is followed by an outpouring of sympathetic activity and a clearly positive relationship has been established between the injury severity score (ISS) and the plasma concentration of adrenaline, noradrenaline and dopamine. The plasma catecholamine levels are maximal shortly after injury, but this response is short lived and the plasma levels have usually returned to the normal range within 24 h. Although it is possible to relate plasma hormonal levels to the ISS score we have recently demonstrated that there is no correlation between the ISS score and the degree of metabolic abnormality seen in patients after blunt trauma. The metabolic response in these patients appears to be an 'all or none' response—the patient with an ISS of 15 is metabolically similar to the patient with a score of 50.

At the same time as the sympathetic nervous system response, the hypothalamic-pituitary axis is also activated. However, the relationship between injury severity and plasma cortisol is not direct: cortisol levels peak at an ISS of 12 and then become lower with more severe injury. In addition, the cortisol response is transient and the plasma cortisol level falls to normal within a few days of injury. Furthermore, the correlation between hormonal changes and metabolic abnormalities is difficult to show; for example we have found no correlation between the plasma cortisol level and the degree of alteration in either glucose or protein kinetics.

The plasma concentration of growth hormone is raised for 24 h after injury, as is that of prolactin. Following thermal injury antidiuretic hormone levels have been reported to be ten times control values. Aldosterone is increased, the renin-angiotensin system is activated and glucagon levels rise markedly about 12 h after major injury.

Thus, the ebb phase of injury is associated with increased sympathetic activity and an outpouring of counter-regulatory hormones. However, during the stage of maximal nitrogen loss in the flow phase (about 7–10 days after injury) the catecholamine, glucagon and cortisol plasma levels are not raised. This is, however, the time when the plasma insulin level rises to a peak.

Although the catabolic response during the postinjury flow phase and established sepsis is similar, there exist differences in the hormonal milieu between these two conditions; the counter-regulatory hormones remain high in septic patients and the elevation of insulin levels is not a consistent feature.

There has been a recent attempt to simulate the hormonal responses associated with injury in normal volunteers to elucidate the role of hormones as mediators of the metabolic changes seen following trauma. Nine volunteers received a continuous 74 h infusion of the three 'stress' hormones.
The post-traumatic ebb phase and the earliest stage of sepsis are both characterized by hyperglycaemia. This rapidly established response is initially the result of enhanced glycogenolysis and a simultaneous release of stress hormones which may be responsible for mediating the metabolic response to injury.

**Inflammatory mediators**

It is not possible to explain the complete spectrum of metabolic changes seen in septic and injured patients by the neuroendocrine response as it is presently understood. This has provoked the search for other mediators. Recent research has suggested that interleukin 1, a protein released by macrophages at sites of inflammation, plays a part in the afferent link between damaged tissue and the central nervous system. This new work is discussed further in relation to protein metabolism (see below).

Wilmore has recently described synergism in the action of inflammatory and endocrine mediators and concluded that both are integral factors of the metabolic response to sepsis and trauma.

**Energy production**

Cuthbertson's appealingly simple description of a hypometabolic ebb phase and hypermetabolic flow phase has undergone substantial modification in the light of more contemporary research. There is little evidence from clinical studies to suggest that heat production is reduced during the ebb phase, and it is likely that the increase in metabolic rate during the flow phase is not as large as previously thought. Nonetheless, the less a modest increase in resting energy expenditure in the flow phase is commonly observed and, in the extreme case of extensive burn injury, this increase may be as great as 100 per cent. The maximal increase in resting energy expenditure coincides with the maximal rate of protein catabolism and occurs around 1 week after injury.

Numerous factors have been proposed to account for the extra heat production, such as the increased oxygen consumption of the injured tissues, increased energy expenditure by the heart, the Q10 effect of raised body temperature, the thermic effect of accelerated protein breakdown and the heat of vaporization lost from burn surfaces. The matter has been the subject of a concise review by Little which concludes that the underlying mechanism is probably a resetting of hypothalamic regulatory control. Yet a further explanation has recently been advanced: it is known that in trauma patients there is an increase in the rate of substrate recycling in which triglyceride is hydrolysed and then re-esterified, and glucose and its glycolytic intermediates are recycled. As there is no net production of free fatty acid or glucose during these cycles but ATP is hydrolysed, such recycling represents an energy drain. Wolfe et al. have recently quantified the energy dissipated by such substrate recycling and, although their methodology grossly underestimates the extent of these processes, they conclude that it is possible that these cycles provide the principal biochemical explanation for the increased heat production seen in trauma patients.

**Glucose metabolism**

The post-traumatic ebb phase and the earliest stage of sepsis are both characterized by hyperglycaemia. This rapidly established response is initially the result of enhanced gluconeogenesis and later a consequence of increased glucose production coupled with reduced peripheral utilization. Sympathetic activity and circulating adrenaline provide the stimulus for hepatic gluconeogenesis and encourage glucagon release while simultaneously inhibiting insulin release from the endocrine pancreas. The release of cortisol probably plays a facilitatory part in this response. The plasma glucose levels subsequently fall during the post-traumatic flow phase to less elevated or normal levels.

However, the plasma glucose level gives little indication of glucose turnover and this has been the subject of much recent investigation. It is generally agreed that in septic and flow phase trauma patients, glucose turnover is increased and that gluconeogenesis is enhanced despite freely available plasma glucose, but there is controversy over changes in glucose oxidation in these situations.

**Gluconeogenesis**

In health, gluconeogenesis is effectively inhibited by an increase in blood glucose levels. However, hepatic glucose production is maintained at normal or elevated rates during the high flow response to trauma or sepsis despite the hyperglycaemia characteristic of such severely ill patients. The suppression of gluconeogenesis by glucose infusion is very much less effective in septic and trauma patients than in normal volunteers. This reduction in the suppressibility of gluconeogenesis is probably caused by the increased availability of gluconeogenic substrates occurring in a favourable hormonal milieu. In severely stressed patients, muscle glycogenolysis and the metabolism of hypoxic tissues produce lactate, glycerol is released from adipose tissue, and plasma alanine levels are increased as a result of enhanced proteolysis. In burn patients it has been determined that lactate is quantitatively the most important gluconeogenic substrate. Recently, we have demonstrated an increase of 40 per cent in the rate of appearance of alanine and a 100 per cent increase in the rate of appearance of glycerol and availability of lactate in trauma patients. On the basis of 2 mol of either alanine, glycerol or lactate being required to produce 1 mol of glucose it is likely that this substantial increase in three carbon substrates would be adequate to explain the observed increase in basal glucose appearance seen in these patients.

However, in recent work by Jahoor et al. in burn patients in which both insulin and glucagon concentrations were lowered simultaneously, infusion of somatostatin, hepatic glucose production decreased despite an increase in the delivery of alanine to the liver. These results suggest that glucose production is controlled at the liver and not by precursor supply.

**Glucose oxidation**

Although most investigators report that glucose oxidation is increased during the high flow phase and sepsis in absolute terms, there remains disagreement over whether glucose is oxidized as efficiently as in healthy volunteers. The Manchester Trauma Unit researchers have found an increase in glucose oxidation in relation to plasma glucose in injured patients, which they interpreted as a consistent response of substrate mobilization and oxidation. However, the situation is far from clear: there exists a considerable body of data derived from isotopically labelled substrate studies which suggests that glucose is oxidized less efficiently in septic and trauma patients. The recently reported reduced activity of the pyruvate dehydrogenase complex in septic rats suggests that intracellular derangements in enzymatically controlled pathways may account for the observed reduced efficiency of glucose metabolism.

It is germane to the interpretation of the data reported on glucose kinetics that the rate of glucose clearance from the plasma is not related to the rate of glucose oxidation or even to the percentage of glucose uptake oxidized. Therefore, it is unlikely that reduced glucose oxidation is simply a consequence of the prevailing insulin resistance.

**Insulin**

Although changes in insulin release and responsiveness in septic and trauma patients have been well documented, the role of this hormone in the metabolic changes associated with these conditions remains to be clearly defined. The sympathetic discharge following severe burns has been associated with an inhibition of insulin release, although a low plasma insulin level is not a consistent feature of the immediate
postinjury period\(^1\). Plasma insulin levels subsequently rise to reach a peak several days after injury of up to three times basal levels\(^2\). This coincides with the period of maximal catabolism\(^3\).

During the flow phase, the plasma insulin level is inappropriately high for the plasma glucose concentration\(^4\) with the pancreas showing a normal or augmented response to glucose infusion\(^5\). However, this phase of the metabolic response is characterized by insulin resistance.

The high levels of insulin fail to suppress glucose production, and there is a reduction in glycogen storage\(^6\), lipolysis and fat oxidation\(^7\). Frayn has demonstrated a highly significant correlation \((r = 0.97)\) between the plasma insulin concentration and nitrogen loss in trauma patients and concludes from this finding that protein turnover is resistant to the normal anabolic effect of insulin\(^8\). However, Jahoor et al. have found in burn patients that insulin acts to conserve protein by restraining the release of amino acids from peripheral tissues\(^9\). Wilmore has similarly demonstrated a protein anabolic effect of insulin despite profound insulin resistance to carbohydrate in the skeletal muscle of injured patients\(^10\). The nature of the changes in insulin receptors has not been accurately characterized, although it is likely that there are changes at both the receptor and post-receptor level\(^11\).

Experimental animal models most closely implicate glucocorticoids as a cause of insulin resistance\(^12\), although the mechanism of this response is yet to be fully elucidated.

The adaptive value of fuel store mobilization

The mobilization of fuel reserves in trauma and sepsis is common to several species of laboratory animal studied and is likely to be of adaptive value. Infusion of hyperinsulinemic glucose has been shown to decrease mortality in pigs following severe haemorrhage\(^13\) and this manoeuvre has also resulted in a rapid increase in blood pressure in recently injured battle casualties\(^14\). It has been suggested that the observed pressor effect is due to a mass action effect of glucose increasing myocardial glucose uptake and hence the availability of glucose for anaerobic glycolysis\(^15\). Hyperglycaemia will also compensate for intra-vascular fluid losses.

The increase in gluconeogenesis and its reduced suppressibility during exogenous glucose administration in the post-trauma flow stage and in sepsis may reflect the influence of the damaged and reparative tissues on the rest of the body\(^16\). The cells involved in inflammation and wound repair rely on glucose as a primary fuel which they predominately metabolize anaerobically. The wound may be looked upon as a privileged organ whose glucose demands can account for most of the approximate doubling in glucose turnover seen in severely burned patients. Wilmore concludes that the increased glucose turnover provides essential fuel for inflammatory and reparative tissue which optimizes host defences and ensures wound repair\(^17\).

Fat metabolism

The complex changes in the mobilization and oxidation of fat in sepsis and trauma have not been as fully unravelled as those in carbohydrate metabolism. Again it is appropriate to discuss the post-trauma changes in the ebb and flow phase, and again there are parallels to be drawn between the flow phase and established sepsis.

Lipolysis is enhanced immediately after injury by the stimulation of the sympathetic innervation of adipose tissues and by raised plasma adrenaline, glucagon and cortisol levels\(^18\). Growth hormone may also play a part in this response\(^19\). The accelerated lipolysis occurs despite the prevailing hyperglycaemia and raised plasma insulin\(^20\). There is, however, little correlation between plasma free fatty acid levels and the severity of the trauma\(^21\). This is probably a result of the reduced perfusion of adipose tissues which often follows severe trauma, so that the supply of albumin carriers for released free fatty acids is inadequate\(^22\). In addition, the plasma free fatty acid level is lowered further by the lactic acidosis of systemic hypoxia which encourages re-esterification\(^23\).

Septic patients have a lower respiratory quotient (RQ) than non-septic controls, and worsening sepsis is frequently accompanied by progressive falls in RQ. These findings have been corroborated by isotopic studies and suggest that increased fat oxidation may be an important feature of the altered metabolism seen in sepsis\(^24\). During the first few days after severe injury the RQ rises from a value of close to 0.7 to one that indicates that carbohydrate is the major fuel\(^25\). Glucose infusion in normal volunteers inhibits fat oxidation and the RQ rises above 1.0 as the excess glucose is deposited as triglyceride. However, in patients with severe sepsis, although the RQ rises following glucose infusion it does not reach a value of 1.0 indicating that fat continues to be the main substrate for oxidation\(^26\).

Under most circumstances the rate of uptake of free fatty acids is directly proportional to their plasma concentration\(^27\). However, the increase in fatty acid oxidation in sepsis and trauma is not "substrate led" as the plasma levels of free fatty acids are often quite low\(^28\). This suggests that there are changes in the intracellular metabolism of fat in these patients\(^29\).

The preference for fat as an energy substrate is more pronounced in sepsis than in trauma patients\(^30\). Using the sepsis severity scale developed by Elebute and Stoner\(^31\), it has been shown that there exists a positive relationship between fat oxidation and sepsis severity, whereas there is a negative relationship with glucose oxidation\(^32\).

Less is known about changes in triglyceride metabolism. It has been reported that the concentration of triglyceride in plasma is elevated in Gram-negative sepsis\(^33\) and after injury\(^34\). There is presently no isotopically-labelled triglyceride suitable for infusion into patients, but studies in septic animals have revealed that the increase in triglyceride concentration is owing to an accelerated rate of production of triglyceride, and in particular very low density lipoprotein, rather than the response being secondary to a decrease in triglyceride clearance\(^35,36\). The increase in activity of adipose tissue lipoprotein lipase is consistent with the postulated increase in very low density lipoprotein turnover\(^37\).

Ketone metabolism

Simple starvation is attended by ketosis. As ketone bodies can serve as alternative energy substrates for many tissues, they reduce whole body glucose demand and therefore gluconeogenesis from protein. However, in severe sepsis and, to a lesser extent, trauma there is a blunting of the adaptive ketonaemic response and its subsequent nitrogen conservation\(^38\). It is likely that the increased insulin levels seen in stressed surgical patients are responsible for the impaired production of ketone bodies\(^39\), although reduced activity of hepatic acetyl-CoA transferase has also been implicated\(^40\).

Protein metabolism

The negative nitrogen balance described by Cuthbertson\(^1\) has been similarly demonstrated in septic patients\(^7\). When this response is prolonged, the resultant protein depletion plays a major part in the pathogenesis of multiple organ failure which develops in severely injured or septic patients\(^7\). A detailed understanding of the nature and mechanism of the protein loss is important to provide a basis for giving more effective nutritional support and offers the alluring possibility of metabolic manipulation in such cases.

Whole body kinetics in sepsis and trauma

A net protein loss may result from a relative decrease in whole body protein synthesis, an increase in catabolism, or a combination of both mechanisms. The varied responses reported following elective surgical procedures, musculoskeletal trauma, burns and sepsis are summarized in Table 1. The trauma
The preceding description of the relative changes in the relationship between net protein synthesis and catabolism oversimplifies the situation as it exists in the clinical setting as it does not include the influence of protein intake. This deficiency is rectified in the model developed by Clague and his colleagues, in which they propose that the protein breakdown in response to trauma is largely obligatory, whereas synthesis increases with substrate availability. Accordingly, provision of adequate protein can reduce net nitrogen loss after trauma.

Changes in skeletal muscle
Skeletal muscle is the major site of nitrogen storage and of nitrogen loss, although the contribution of other tissues such as skin, gut and lungs may not be insubstantial. The rate of release of 3-methylhistidine, an amino acid derived exclusively from actin and myosin and excreted unchanged, has been used as an index of the rate of skeletal muscle breakdown. Considerable increases in the rate of production of 3-methylhistidine have been seen in severely traumatized and septic patients, whereas no increase occurs following orthopaedic operations and minor injuries. Although recent doubts have been voiced about the specificity of 3-methylhistidine as an indicator of skeletal muscle breakdown, other investigators have provided sound arguments for its continued use.

In injury, the increased rate of protein release from skeletal muscle does not simply represent the degradation of damaged tissue; there is increased loss of 3-methylhistidine and changes in skeletal metabolism in muscle undamaged by trauma.

The technique of percutaneous needle biopsy of human muscle has enabled investigation of the intracellular metabolic derangements. The changes in intracellular amino acid concentration following elective surgery, trauma and in sepsis are similar, suggesting a common response to varying types of insult. The response consists of an increase in essential amino acids, particularly branched chain amino acids, and reduction in non-essential amino acids largely as a result of a 50 per cent decrease in the level of intracellular glutamine. The cause of these changes remains a matter for conjecture.

Hepatic protein metabolism
The data of studies of whole body protein metabolism represent the summation of response of the body tissues, but fail to reflect variation in kinetics between different tissues. In both severe trauma and sepsis, whereas skeletal muscle catabolism exceeds...
40 g nitrogen a day!!3, they exhaust their energy and protein healing26. It is for these reasons that attempts have been made to provide adequate energy substrates and amino acids for hepatic protein synthesis. However, if ibuprofen or cyclo-oxygenase inhibitors does not reduce muscle catabolism in septic or thermal injury models in animals125.129 or in septic patients126. In our laboratory we have studied the effects of cyclo-oxygenase inhibitors in 23 patients who had recently undergone extensive surgical procedures125. There was a 20 per cent decrease in the rate of production of glucose with a parallel reduction in glucose oxidation, and net protein catabolism as measured by the rate of appearance of [14C]urea was reduced by 11 per cent.

The sympathetic response may also be attenuated with specific pharmacological antagonists. Sympatholytic drugs have been demonstrated to reduce the degree of hypermetabolism in burn patients126. In our laboratory we have studied the effects of $\alpha$ and $\beta$ blockade produced by infusions of phentolamine and propranolol respectively in stressed patients receiving intravenous nutrition127. Our data demonstrate that the role of the sympathetic nervous system in the promotion of endogenous glucose turnover in septic patients is primarily a $\beta$-adrenergic effect, whereas the promotion of protein catabolism is mainly an $\alpha$-adrenergic effect.

Considerable interest in the role of prostaglandins as effectors of the stress response has been aroused by the recent work on interleukin 1. However, decreasing prostaglandin synthesis with cyclo-oxygenase inhibitors does not reduce muscle catabolism in septic or thermal injury models in animals128,129 or in septic patients130, and their use exposes patients to side-effects such as septic ulceration and impaired haemostasis.
The use of anabolic hormones to attenuate the rate of breakdown of body reserves is an appealing proposition. Insulin has been shown to improve nitrogen balance in trauma patients\(^{130}\), but was found to have no effect on the gain of body nitrogen or fat when used as an adjuvant with a 2-week course of IVN\(^{131}\). Similarly, anabolic steroids have improved the nitrogen balance in postoperative patients\(^{132}\), but have not been demonstrated to improve the efficacy of IVN\(^{133}\).

Interest in the therapeutic role of human growth hormone has increased since 1985 when gene recombinant technology enabled its manufacture on a scale which makes its use as a pharmaceutical agent feasible. Several early investigators reported improved nitrogen balance in burn patients to whom growth hormone was administered\(^{134-136}\). More recently Ward and colleagues have demonstrated a favourable influence of growth hormone on protein kinetics in postoperative patients\(^{137}\). However, the therapeutic role of growth hormone in catabolic patients awaits further definition.

**Discussion (Figure 3)**

The increased release of hormones, particularly adrenaline, glucagon and cortisol, mediate many of the metabolic changes seen in sepsis and trauma. The role of interleukin 1 has yet to be precisely defined, but there is increasing evidence that substances released from damaged tissue are at least partly responsible for the accelerated proteolysis seen in severe surgical illness.

Glucose turnover is increased in sepsis and trauma, but glucose is oxidized with reduced efficiency. There is evidence to suggest that fat is the preferred energy substrate in septic and, to a lesser degree, injured patients.

In critical surgical illness the rates of both protein synthesis and catabolism are increased. However, the increase in catabolism is of greater magnitude resulting in a net breakdown of protein and, if prolonged, muscular wasting, cardiopulmonary insufficiency and immune compromise.

The provision of sufficient energy substrates and nitrogen does not reduce the catabolic response but encourages protein synthesis, decreasing net catabolism. Numerous substrate, hormonal and pharmacological manipulations have been tried to improve the nitrogen balance in surgical patients who are severely ill. To date, the clinical efficacy of none has been conclusively proved.

**References**


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